



US009194005B2

(12) **United States Patent**
Liao et al.

(10) **Patent No.:** US 9,194,005 B2
(45) **Date of Patent:** Nov. 24, 2015

(54) **METHODS AND BIOMARKER FOR EVALUATING CANCER METASTASIS, PHARMACEUTICAL COMPOSITION FOR INHIBITING CANCER METASTASIS, AND METHOD FOR ANALYZING SECRETOME**

(71) Applicant: **National Cheng Kung University, Tainan (TW)**

(72) Inventors: **Pao-Chi Liao, Tainan (TW); Ying-Hwa Chang, Taipei (TW); Shu-Hui Lee, Changhua County (TW); Hua-Chien Chang, Tainan (TW); Yau-Lin Tseng, Tainan (TW); Wu-Wei Lai, Tainan (TW)**

(73) Assignee: **NATIONAL CHENG KUNG UNIVERSITY, Tainan (TW)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 25 days.

(21) Appl. No.: **14/028,861**

(22) Filed: **Sep. 17, 2013**

(65) **Prior Publication Data**

US 2014/0120528 A1 May 1, 2014

(30) **Foreign Application Priority Data**

Oct. 31, 2012 (TW) 101140274 A

(51) **Int. Cl.**

C12N 15/113 (2010.01)
C12Q 1/68 (2006.01)
G01N 33/574 (2006.01)

(52) **U.S. Cl.**
CPC **C12Q 1/6886** (2013.01); **G01N 33/57423** (2013.01); **C12Q 2600/118** (2013.01); **C12Q 2600/158** (2013.01); **G01N 2570/00** (2013.01)

(58) **Field of Classification Search**

None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2005/0137155 A1 * 6/2005 McSwiggen et al. 514/44

OTHER PUBLICATIONS

Eltoweissy et al, Proteomics analysis identifies PARK7 as an important player for renal cell resistance and survival under oxidative stress, published online Feb. 2011, Mol.BioSyst., 7: 1277-88.*

* cited by examiner

Primary Examiner — Tracy Vivlemore

Assistant Examiner — Kate Poliakova-Georgantas

(74) *Attorney, Agent, or Firm* — Bacon & Thomas, PLLC

(57) **ABSTRACT**

The invention relates to methods and biomarker for evaluating cancer metastasis, pharmaceutical composition for inhibiting cancer metastasis, and method for analyzing secretome. By combining a hollow fiber cartridge (HFC) culture system with quantitative proteomics technology, cancer metastasis-related secretomes can be found. Furthermore, this is the first time to use PARK7 as a biomarker for judging the process of non-small cell lung cancer.

1 Claim, 16 Drawing Sheets

before serum-free
medium adaptation



after serum-free
medium adaptation

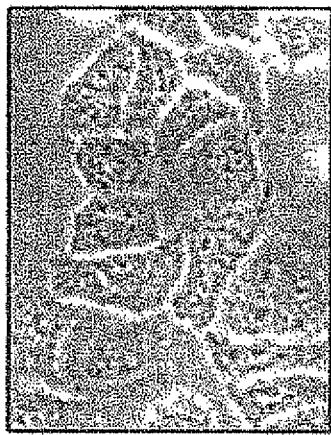


CL1-5

FIG. 1A

CL1-0

200X



200X

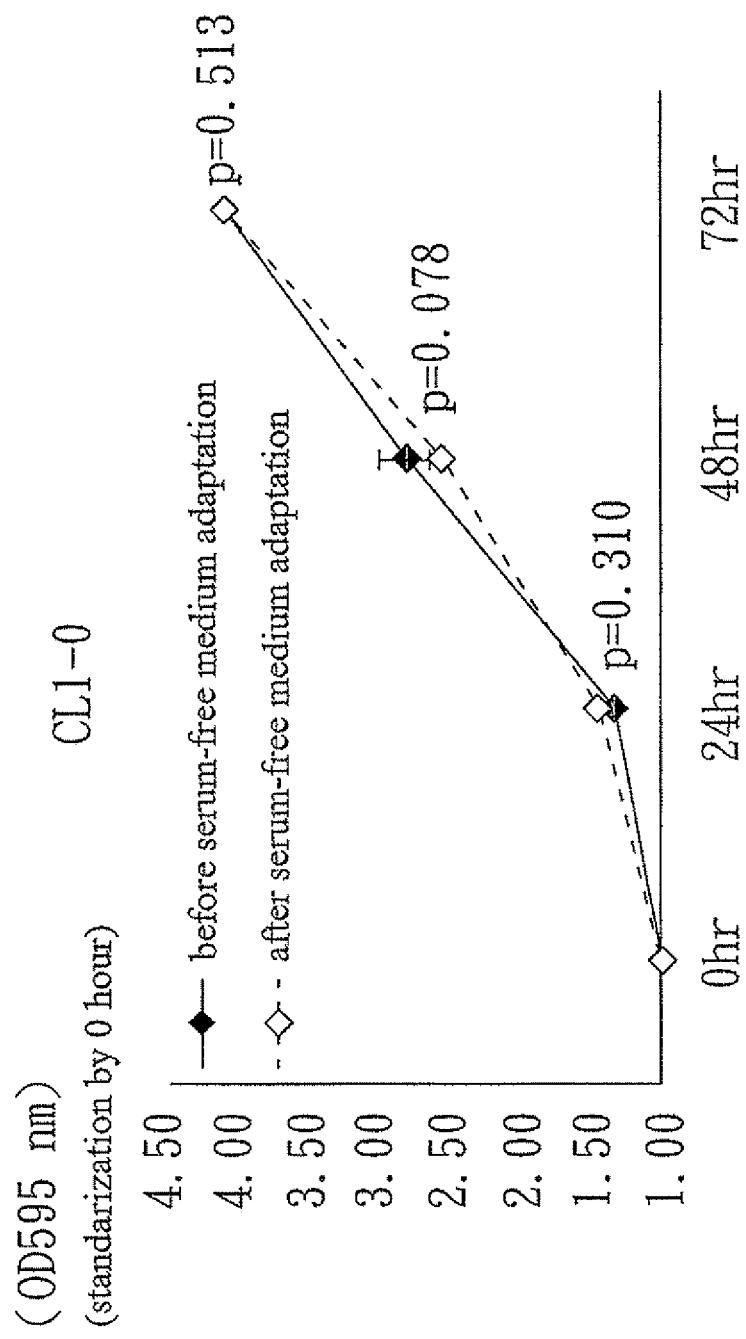


FIG.1B

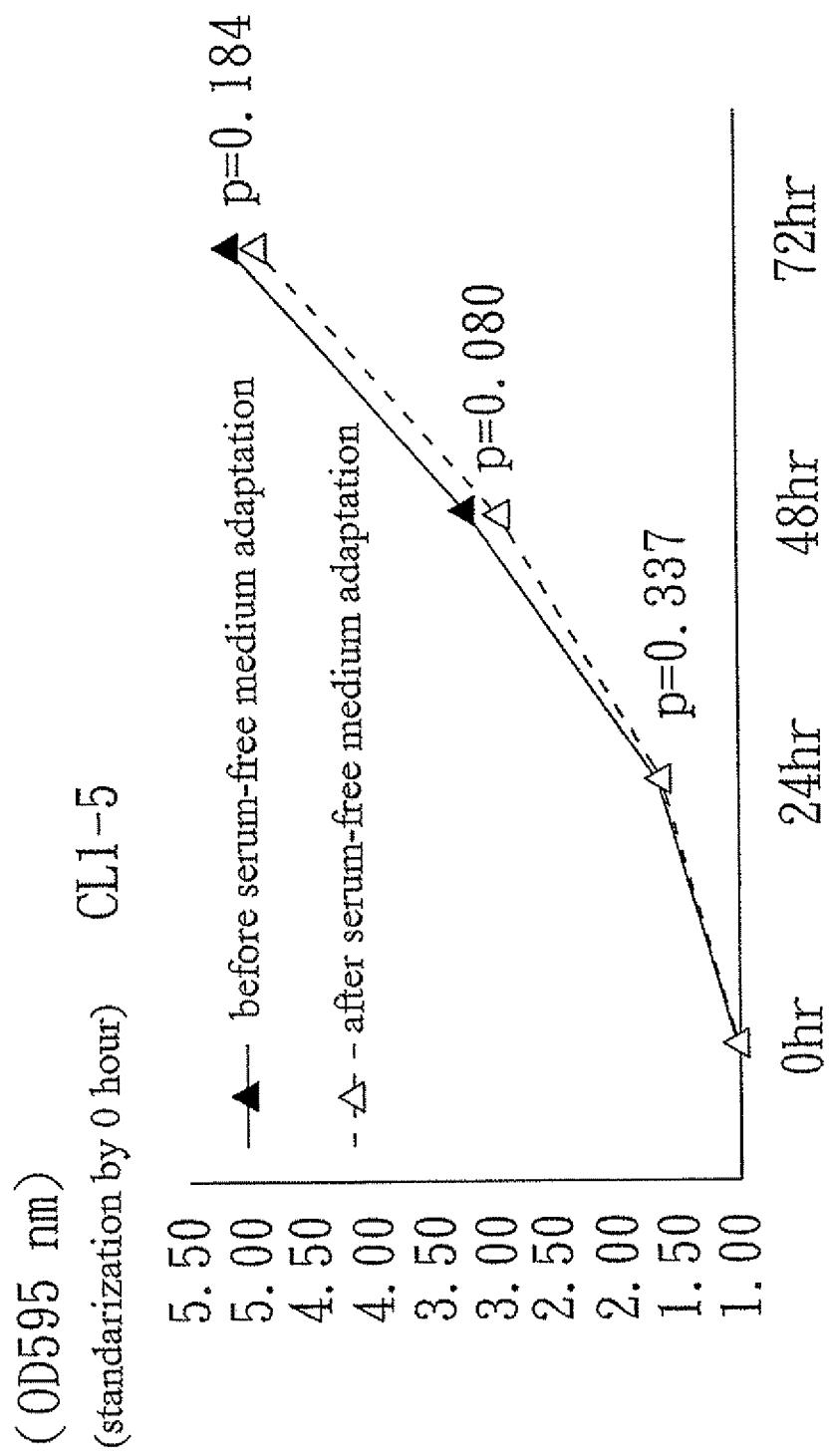


FIG.1C

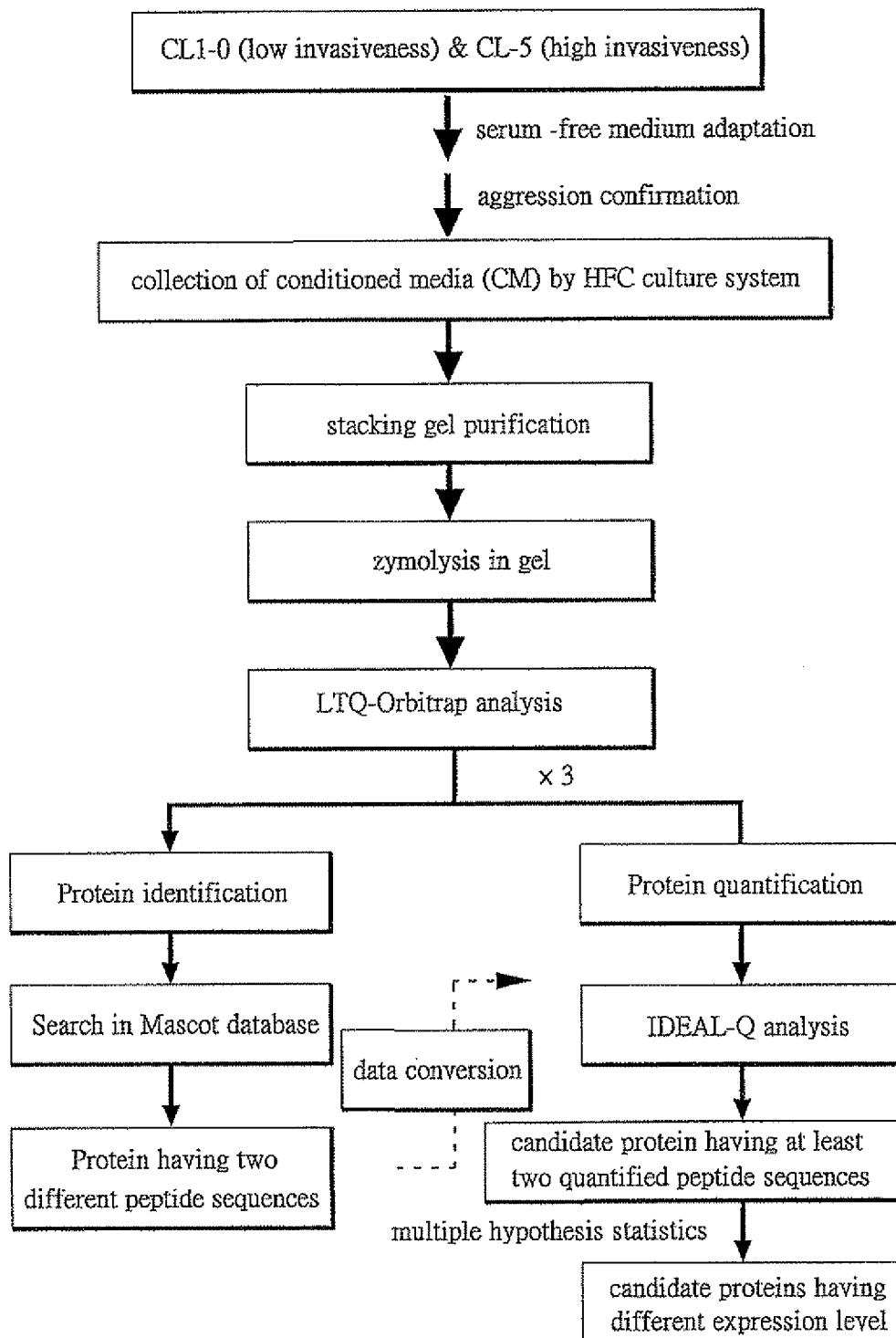


FIG.2

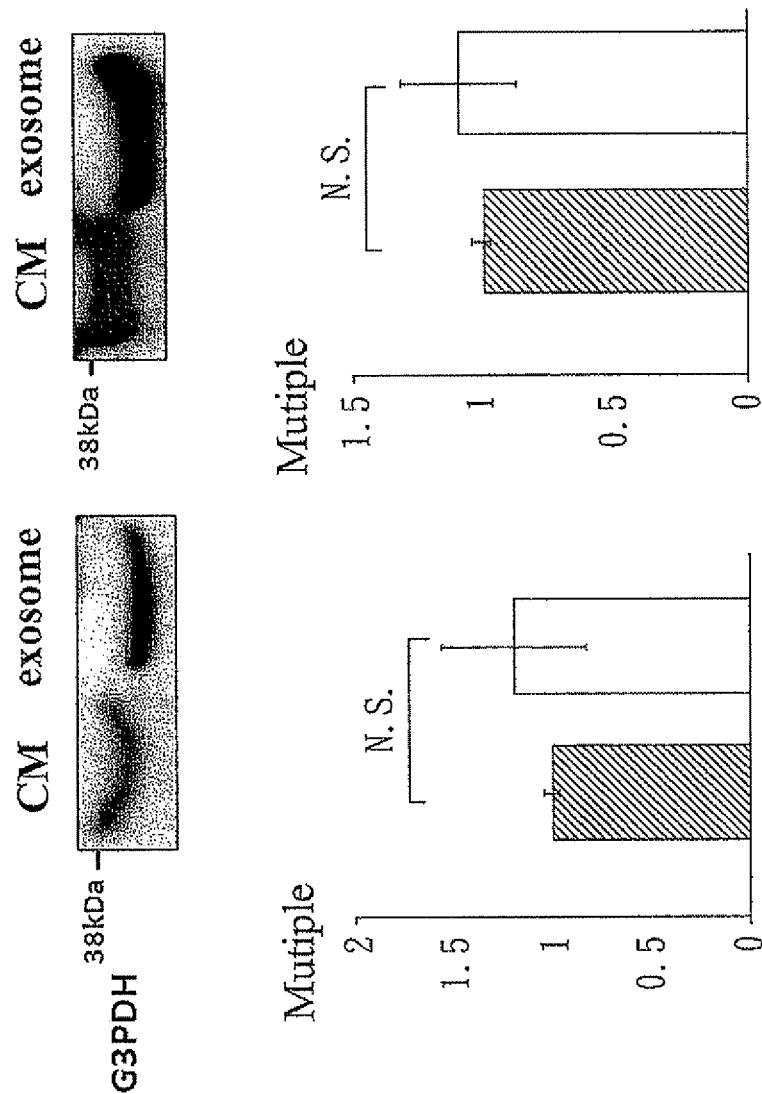


FIG.3

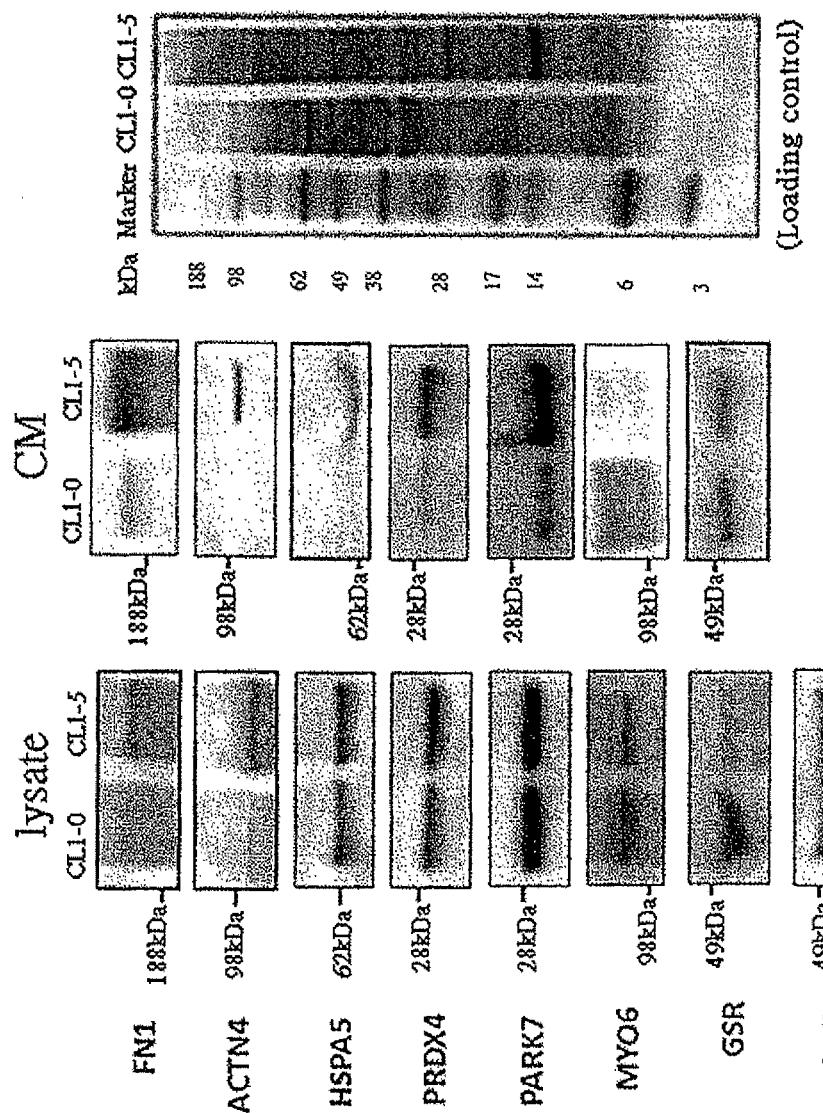


FIG.4

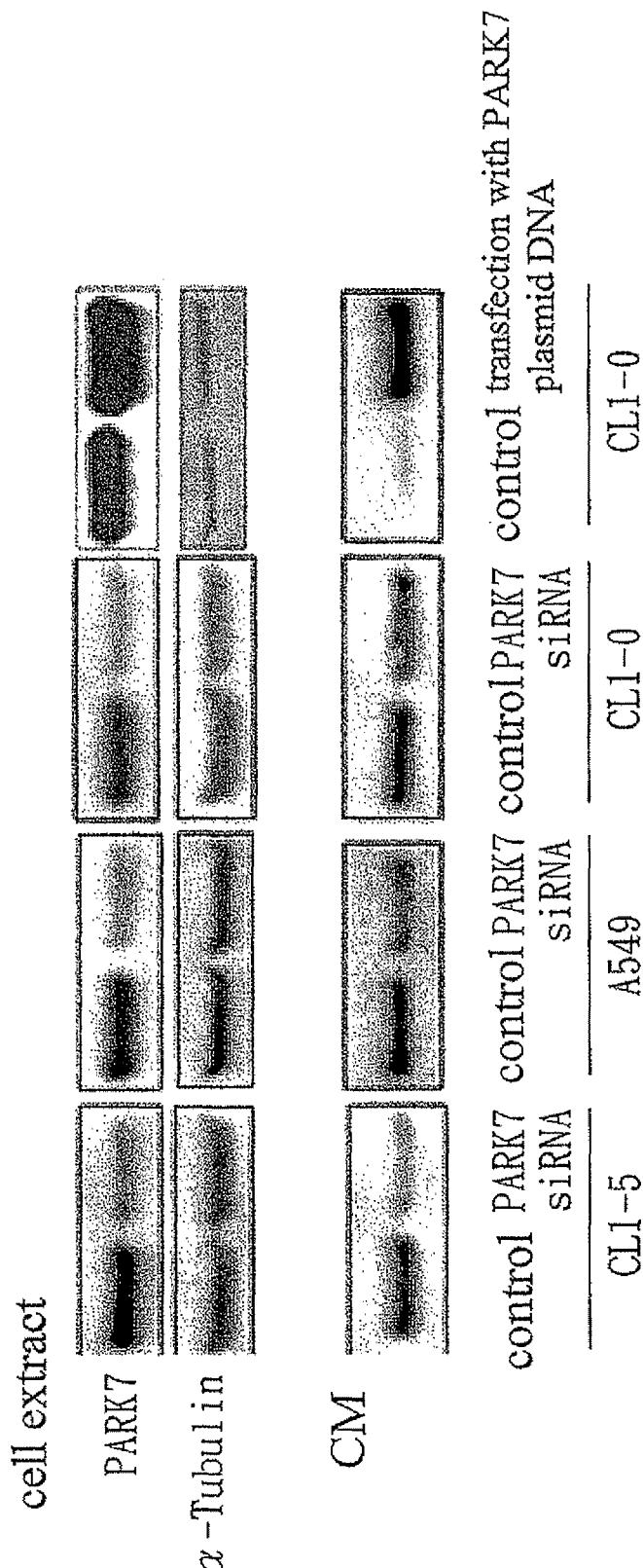


FIG.5A

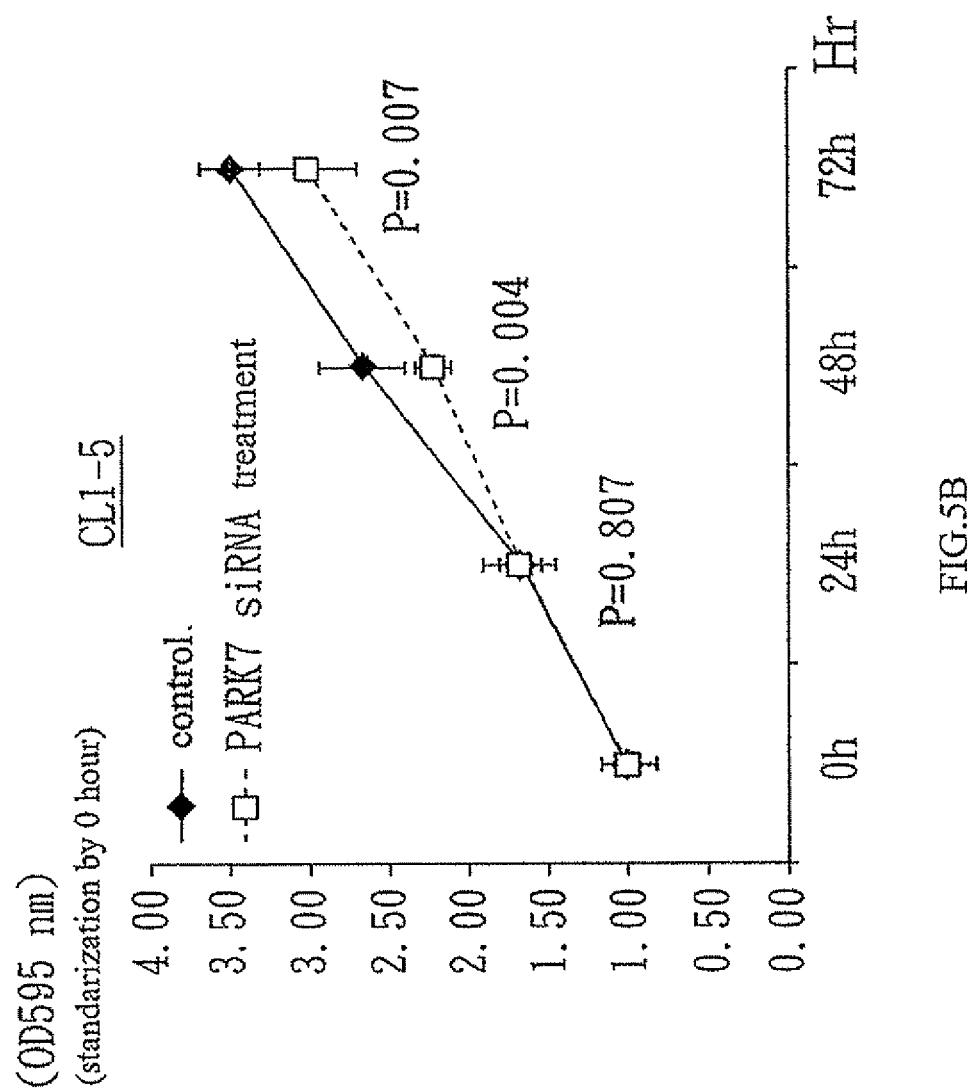


FIG.5B

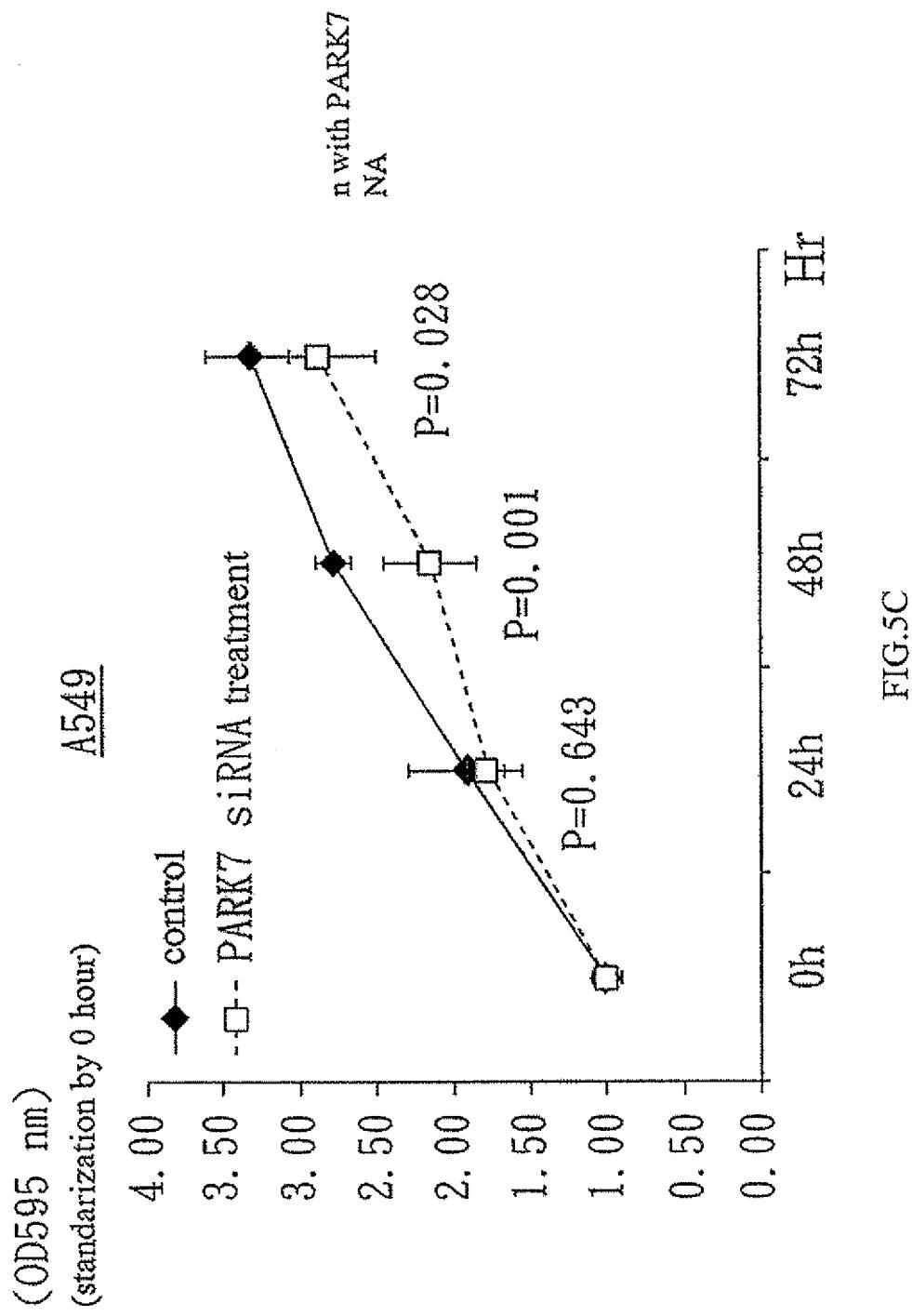


FIG.5C

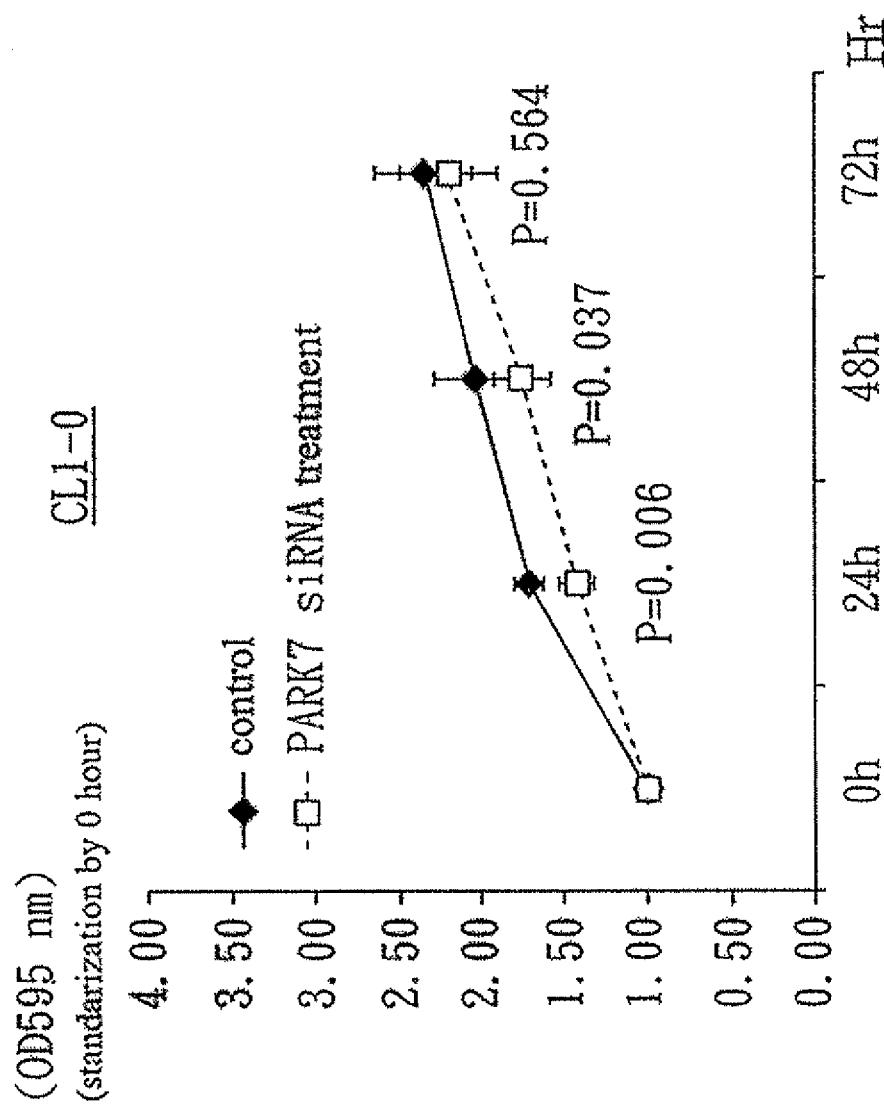


FIG.5D

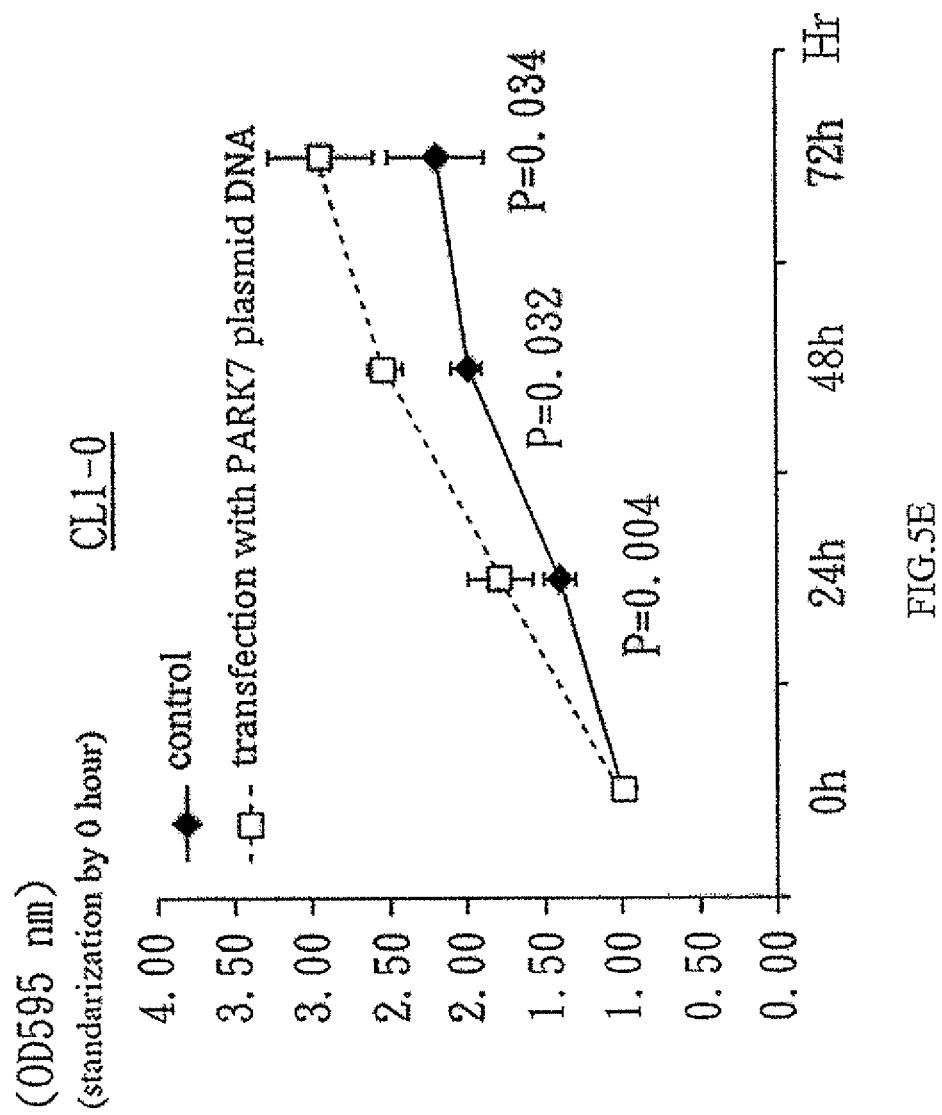


FIG.5E

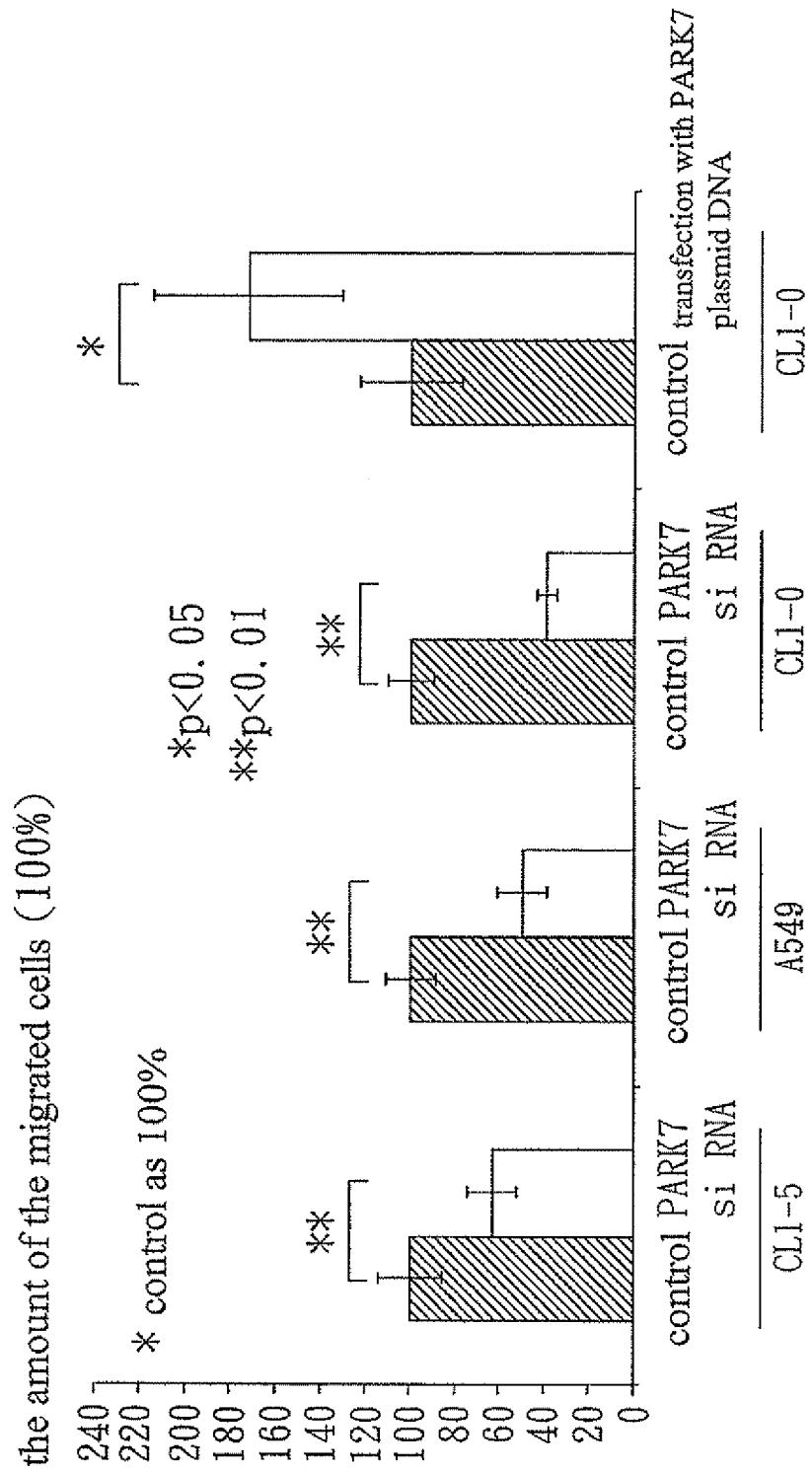


FIG.5F

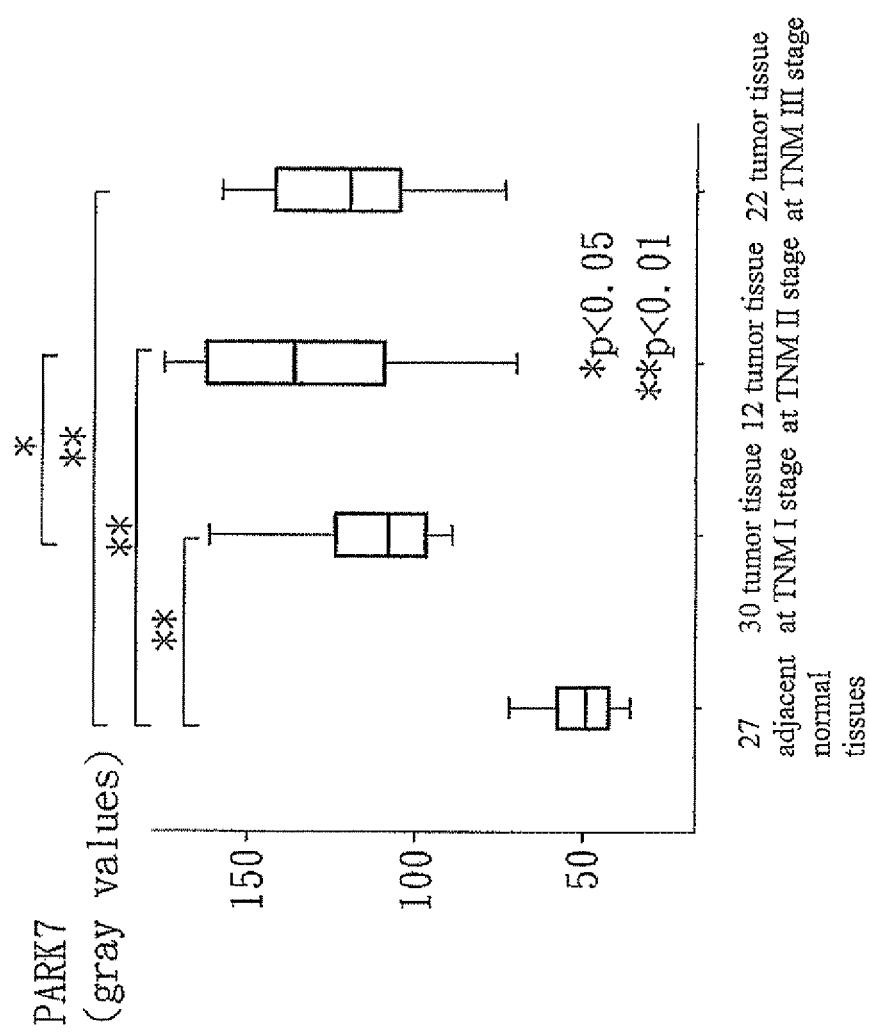


FIG. 6A

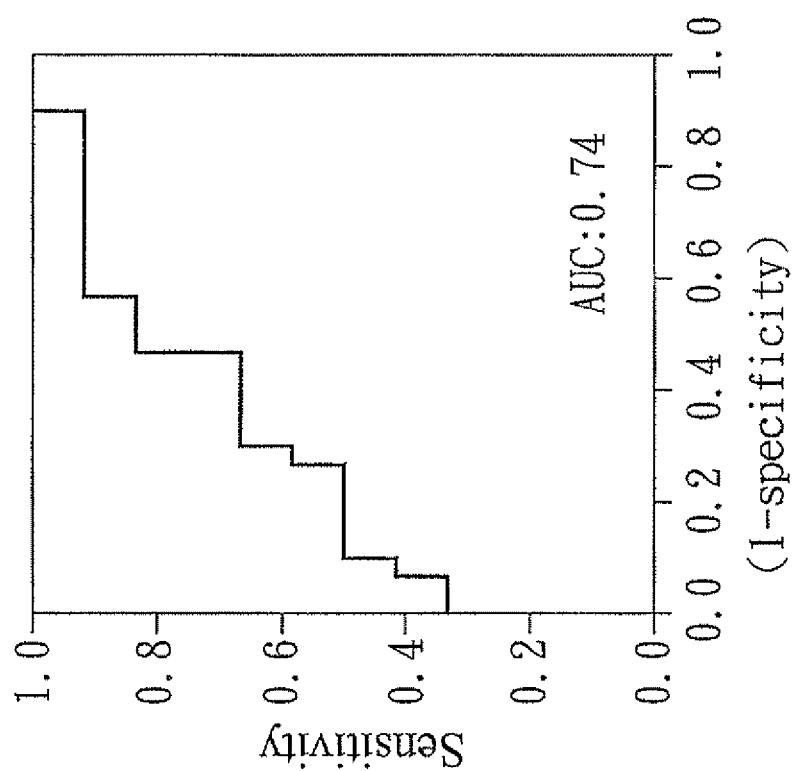


FIG.6B

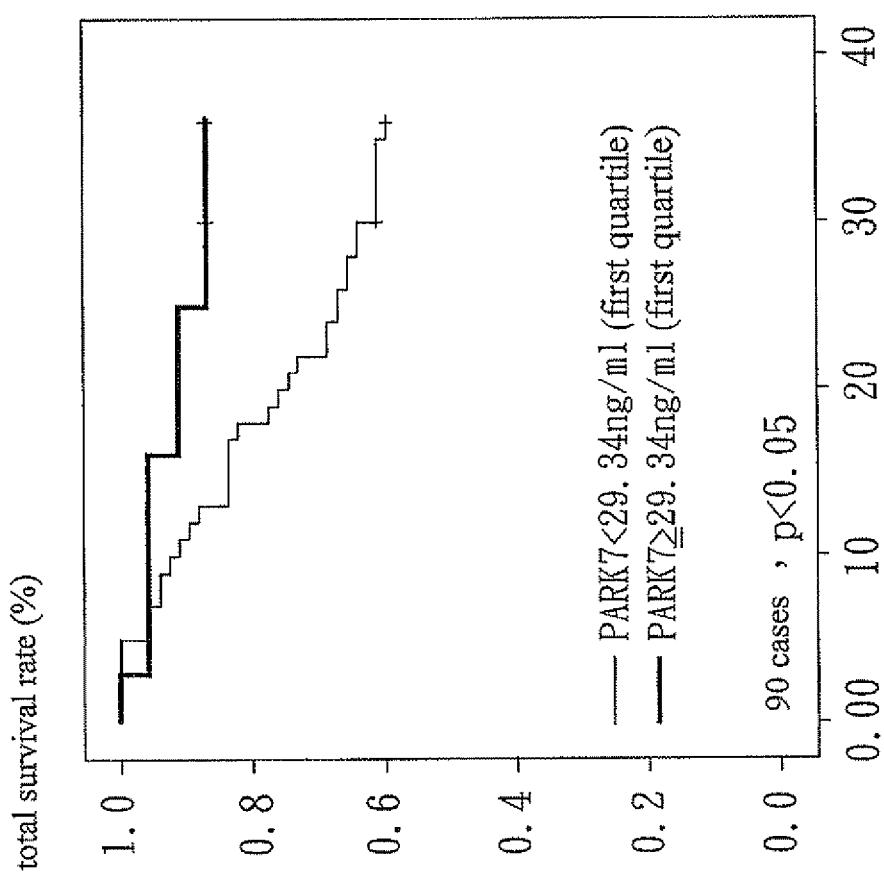


FIG.6C

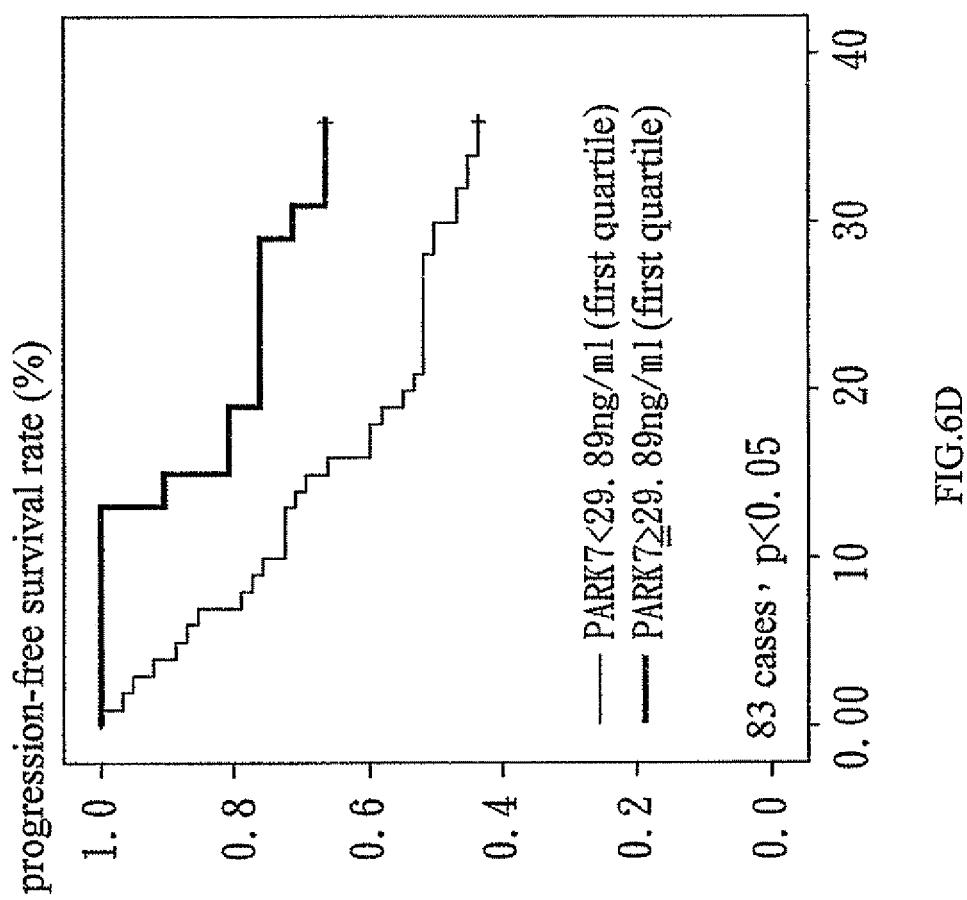


FIG.6D

1

**METHODS AND BIOMARKER FOR
EVALUATING CANCER METASTASIS,
PHARMACEUTICAL COMPOSITION FOR
INHIBITING CANCER METASTASIS, AND
METHOD FOR ANALYZING SECRETOME**

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates a method for evaluating lung cancer metastasis, a biomarker for evaluating lung cancer metastasis, a siRNA compound for inhibiting lung cancer metastasis, and a method for analyzing secretome.

2. Description of Related Art

Cancer, also known as malignant neoplasm, is a disease involving failed mechanism of cell growth proliferation. Lung cancer is the most common cause of cancer death in the world, and some remarkable problems that get in the way of treating lung cancer are that there is low abundance of effective prognosis tools, and low abundance of prevention-oriented treatment methods for keeping off metastasis. In terms of the most popular type of occurring cancer by number of patients, non-small cell lung cancer (NSCLC) accounts for approximately 85% of the demographics, and among all the histological types of NSCLC, lung adenocarcinoma is the most common type. Many lung cancer patients are diagnosed with distant metastatic, and most of them die as a result of the metastases instead of due to the original tumors. The survival rate of lung cancer patients within a 5 year time frame during treatment period is 15.2% and only 2.8% for lung cancer patients complicated by distant metastases. Metastasis is clearly a fatal condition adversely affecting malignant tumor development. Unfortunately, current technologies in clinical practice cannot keep up to solve this problem as there is still low abundance of effective diagnostic and prognostic tools for metastasis and other progression predictions. To further increase patients' survival rates, studies related to the mechanisms of metastasis are of immediate importance.

Metastasis, the ultimate event in a cancer progression, can be described as the complex process in which cancer cells travel from a tumor site and migrate through the bloodstream or lymphatic system to other parts of the body. During this intricate process, numerous proteins are required to assist in the progression of the tumor cells. For example, secretory proteins, which are released from cells via various pathways, including the classical ER-golgi pathway, vesicle release, or a specific channel, are known as the secretome. In previous research, cell secretome was widely used via proteomics technologies in cancer research. There are three main aspects of this research, including discovering clinical biomarker, understanding mechanisms of cancer progression, and planning cancer treatment strategy. Previously, there are many studies reporting that some biomarkers are associated with cancer metastasis and aggression and angiogenesis, such as the proteinase MMP-9 and VEGF respectively.

However, modern technology and the discovered biomarkers still have their shortcomings for cancer metastasis and cancer development process prediction. Therefore, there is still room for people in the art to develop and improve prediction accuracy as well as technical aspects.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a method for evaluating lung cancer metastasis, comprising: (A) providing a specimen sample of a subject, wherein the specimen sample comprises a normal tissue and a tumor tissue to be

2

tested; (B) testing expressions of a biomarker in the normal tissue and in the tumor tissue that is pending to be tested respectively, wherein the biomarker is a genotype or a protein of Parkinson disease type 7 (PARK7); (C) comparing the expressions of the biomarker in the normal tissue and the tumor tissue that is pending to be tested, wherein when the expression of the biomarker in the tumor tissue that is pending to be tested is less than that in the normal tissue, it indicates that the subject is subjected to a cancer metastasis risk.

10 In the step (A), the tumor tissue may be, for example, cell tissue, blood, body fluid or protein, but the tumor tissue for the present invention is not limited thereto.

Particularly, in the step (B), mRNA expression, protein expression, protein derivative expression, or peptide chain expression of proteins of PARK7 in the normal tissue and the tumor tissue to be tested were tested respectively.

15 Preferably, in the step (B), protein expression of PARK7 in the normal tissue and the tumor tissue to be tested were tested respectively.

20 In the method for evaluating lung cancer metastasis of the present invention, wherein, protein expression of PARK7 in the normal tissue and the tumor tissue to be tested are tested respectively by enzyme-linked immunosorbent assay (ELISA), immunohistochemistry (IHC), immunoprecipitation (IP), or mass spectrometry (MS).

In the method for evaluating lung cancer metastasis according to the present invention, the lung cancer particularly refers to non-small cell lung cancer (NSCLC).

25 The present invention also provides a biomarker for evaluating lung cancer metastasis, which may be a nucleotide sequence of PARK7, a complementary strand of the nucleotide sequence of PARK7, a derivative of an oligonucleotide sequence of PARK7, a protein sequence of PARK7, a derivative of the protein sequence of PARK7, a fragment of the protein sequence of PARK7, a variant of the protein sequence of PARK7, or an antibody corresponding to the protein sequence of PARK7.

30 Particularly, the biomarker for evaluating lung cancer metastasis according to the present invention is a protein sequence of PARK7, a derivative of the protein sequence of PARK7, a fragment of the protein sequence of PARK7, a variant of the protein sequence of PARK7, and an antibody corresponding to the protein sequence of PARK7.

35 The biomarker PARK7 for evaluating lung cancer metastasis according to the present invention may serve as a biomarker for cancer risk assessment, cancer diagnosis, and cancer progression prediction, wherein the nucleotide sequence of PARK7 is a sequence represented by SEQ ID NO: 1.

40 In the case of the biomarker for evaluating lung cancer metastasis according to the present invention, the protein sequence of PARK7 is a sequence represented by SEQ ID NO: 2.

45 Another object of the present invention is to provide an siRNA compound for inhibiting lung cancer metastasis, comprising a target sequence selected from a gene of PARK7.

50 Particularly, the target sequence comprises 20-25 oligonucleotides.

55 Particularly, the nucleotide sequence of PARK7 is a sequence represented by SEQ ID NO: 1.

60 Another object of the present invention is to provide a method for analyzing secretome, comprising the following steps: (A) providing a hollow fiber cartridge (HFC) culture system comprising one or a plurality of hollow fiber cartridges (HFC), a circulation pump, a culture medium supply unit, and a discharge unit, wherein two opposite ends of the circulation pump are connected to the hollow fiber cartridges and the culture medium supply unit respectively; two oppo-

site ends of the hollow fiber cartridges are connected to the circulation pump and the discharge unit respectively; culture medium in the culture medium supply unit is supplied to the hollow fiber cartridges by the circulation pump, and the culture medium flowing through the hollow fiber cartridges is discharged by the discharge unit; (B) culturing a cell pending to be analyzed in the hollow fiber cartridge (HFC) culture system, wherein the cell to be analyzed is cultured on the hollow fiber cartridges; (C) collecting secretomes secreted by the cell to be analyzed; and (D) purifying the secretomes and analyzing protein types thereof before comparing the obtained protein types against a proteome database.

The HFC culture system can provide a three-dimensional (3D) space and a circulating environment for cell growth. The hollow fiber cartridge (HFC) culture system is a non-stationary system, it operates to employ the high surface area of the HFC to emulate a three-dimensional intra-body environment to grow cells, lending itself to improve cell growth. This system allows cell metabolite to be discharged, which effects decrease of cell mortality, and obtainment of sufficient amount of the secretomes by way of small-volume sampling, which helps analysis of the secretomes.

According to the method for analyzing secretome of the present invention, particularly, in the step (D), the secretomes is analyzed by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS).

In the method for analyzing secretome of the present invention, in the step (D), purifying the secretomes and discretionally marking the secretomes, to analyze the protein types thereof.

In the event that the secretomes is not marked, protein in the secretomes is analyzed for the protein's m/z, charge, and retention time.

In addition, in the method for analyzing secretome of the present invention, the culture medium for the hollow fiber cartridge (HFC) culture system is a serum-free medium (SFM) or a serum medium. In the interest of avoiding serum contamination or serum replacement from factoring into cell growth, serum-free medium is preferred or serum replacement from factoring into cell growth, serum-free medium is preferred.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A shows the micrographs (200 \times) of the morphologies of the CL1-0 and CL1-5 cells before and after serum-free medium (SFM) adaptation, which were observed by a microscope (200 \times).

FIG. 1B shows the proliferation of the CL1-0 cells before and after serum-free medium (SFM) adaptation, which was investigated via MTT assay.

FIG. 1C shows the proliferation of the CL1-5 cells before and after serum-free medium (SFM) adaptation, which was investigated via MTT assay.

FIG. 2 shows the experimental workflow of secretomes analyses for lung adenocarcinoma metastasis according to an example of the present invention.

FIG. 3 shows different expression levels of the housekeeping protein G3PDH with and without exosome purification in an identical amount of CM.

FIG. 4 shows the comparison of candidate protein expressions in CL1-0 and CL1-5 via Western blot according to an example of the present invention.

FIG. 5A shows the PARK7 protein expressions in cells treated with PARK7 siRNA or the plasmids transfected with PARK7 DNA according to an example of the present invention.

FIG. 5B shows the proliferation of the CL1-5 cell line treated with PARK7 siRNA according to an example of the present invention.

FIG. 5C shows the proliferation of the A549 cell line treated with PARK7 siRNA according to an example of the present invention.

FIG. 5D shows the proliferation of the CL1-0 cell line treated with PARK7 siRNA according to an example of the present invention.

10 FIG. 5E shows the proliferation of the CL1-0 cell line treated with the plasmids transfected with PARK7 DNA according to an example of the present invention.

15 FIG. 5F shows the amount of the migrated CL1-5, A549 and CL1-0 cells respectively in each region according to an example of the present invention.

FIG. 6A shows the expression levels of PARK7 between adjacent normal tissue specimens and cancerous tissues with overall TNM stages I, II, and III, wherein the statistical difference therebetween was obtained.

20 FIG. 6B shows the receiver operating characteristic (ROC) curve according to tissue specimens of the present invention, wherein TNM stages I and II are clearly distinguished.

FIG. 6C shows the Kaplan Meier estimator of the survival rates according to the plasma samples of the present invention.

25 FIG. 6D shows the Kaplan Meier estimator of the progression-free survival rates according to the plasma samples of the present invention.

30 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Hereinafter, preferred embodiments of the present invention will be described in detail with reference to the accompanying drawings. However, the present invention is not limited to the embodiments disclosed below, but can be implemented in various forms. The following embodiments are described in order to enable those of ordinary skill in the art to embody and practice the present invention, and those skilled in the art will appreciate that various modifications, additions and substitutions are possible without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

Hereinafter, the lung adenocarcinoma cell line will be used 45 as an example to describe a specific embodiment of the present invention in detail, and reference to the flow chart (FIG. 2) is required so the present invention can be more easily understood and applied.

Harvesting Conditioned Media from CL1 Cancer Cell Lines Using a Hollow Fiber Cartridge (HFC) Culture System

In this example, the lung adenocarcinoma cell lines CL1-0 (lowly invasive) and CL1-5 (highly invasive) derived from the same parental cell line with low and high invasive abilities respectively were provided and cultured in RPMI-1640 55 media supplemented with 10% fetal bovine serum (FBS). The volume of serum medium was slowly reduced and replaced with serum-free medium consisting of RPMI 1640 with 15% CDM-HD serum replacement and 1% antibiotics. Following 2-3 passages, the morphologies of cell lines CL1-0 and CL1-5 60 (FIG. 1A) were observed with a microscope (200 \times), and the cell growth status was tested by MTT technology, referring to FIGS. 1B, 1C. Our results demonstrated that the morphologies and growing conditions for the CL1-0 and CL1-5 cells did not change significantly after SFM adaptation, compared to cells grown in serum medium. After that, the adapted cells were transferred to hollow fiber cartridge (HFC) culture system.

5

Next, CL1-0 and CL1-5 cells ($\sim 5 \times 10^7$) were suspended in serum-free medium then inoculated into the extra-capillary space (ECS) of the hollow fiber cartridge. 15 mL of secretome samples in conditioned media (CM) from the extra-capillary space (ECS) of the hollow fiber cartridge (HFC) culture system were collected every 24 hrs. The media used for maintaining cell growth was refreshed every day. In addition, glucose and lactate concentrations were also measured daily to monitor cell growth in the hollow fiber cartridge (HFC) culture system.

CM harvested from the ECS of the hollow fiber cartridge (HFC) culture system was ultracentrifuged at 10000×g for an hour to remove cell debris. Then, the protein concentrations of the secretome samples were determined using the Bradford assay (Bio-Rad, Hercules, Calif., USA).

In order to confirm that the intracellular proteins were come from the cell secretion rather than via cell lysis, a total of 100 m of CM sample was equally separated into two parts. One of the CM parts was used for exosome purification, to be compared against the housekeeping protein G3PDH between the CM samples (50 µg) applied to exosome purification and another CM part (50 µg). Referring to FIG. 3, the G3PDH protein appeared in similar amounts between the CM sample (50 µg) and exosome fraction. These results confirm that intracellular proteins were released into the extracellular space via exosome secretion.

Sample Purification and Analysis

The stacking gel-aided purification method was previously established in the conventional knowledge for use in secretome sample clean-up, wherein the CM samples were mixed with the sample dye and 0.5 M DTT before being added into a self-poured stacking gel that contained 50% running gel and a 4% stacking gel. Then, SDS-PAGE was performed at 55 V for 30 min. The protein samples were stacked to the border between the stacking and running gel.

In this example, the CM samples during the second to tenth day of cell growth were collected, and then the protein in the CM sample of CL1-0 and CL1-5 CM cells were recovered using the stacking gel-aided purification method for uses in subsequent experiments of staining and hydrolyzing colloid into peptide fragments.

Coomassie Brilliant Blue R-250 was used to stain the gel. All bands were excised and digested in-gel with trypsin. The gel pieces were reduced with 0.5 M DTT (56° C.) and alkylated with saturated iodoacetamide at room temperature, with each step requiring 1 hr.

20 µL of 0.1 µg/µL of modified trypsin was added to the gel pieces, and they were incubated overnight at 37° C. The digested peptide samples were purified with a C18 tip followed by mass spectrometry analyses.

Mass Spectrometry Analyses

In the present example, the MS samples of CL1-0 and CL1-5 CM cells were analyzed using a LTQ-Orbitrap hybrid mass spectrometer with a nanoelectrospray ion source (Nanoelectrospray, branded under ThermoElectron, San Jose Calif.) coupled to a nano flow HPLC (Nanoflow HPLC, branded under Agilent Technologies 1200 series).

Protein Identification and Quantification

In the protein identification of the present example, searching with the Mascot database search was performed, and a protein was selected if it had at least two unique peptide sequences that could be quantified, where in the two peptide sequence defined as RANK 1 are the candidate protein of the present invention. A total of 412 and 531 proteins were identified in CL1-0 and CL1-5 cells, respectively. Subsequently, identified proteins were quantified via IDEAL-Q software.

6

Next, protein quantification was performed in terms of the candidate protein's m/z, charge, and retention time in the LC-MS/MS analysis, using IDEAL-Q software. By means of this method, a total of 50 candidate proteins were identified with different levels between CL1-0 and CL1-5 cell lines. Among these proteins, 25 and 25 proteins exhibited high levels in the CL1-0 and CL1-5 cells, respectively.

Selection of Protein Candidates Via Interactome Analysis

Next, interactions between the 50 candidate proteins were 10 analyzed using the STRING 9.0 database and 7 proteins were selected based on these results. The proteins ACTN4, FN1, PARK7, PRDX4 and GRP78 within the highly invasive CL1-5 cells were expressed at high levels, and proteins MYO6 and GSR within the lowly invasive CL1-0 cells were 15 expressed at high levels.

In this example, as shown in FIG. 4, the 7 protein levels were further analyzed via western blot (the housekeeping protein tubulin as a control). The findings produced by the western blot analysis and the mass spectrometry data were 20 compared against each other to analyze for consistency.

In this case, the results of PARK7 from the western blot analysis and from the mass spectrometry PARK7 were consistent with each other, this confirms that PARK7 has high levels of expression in CL1-5 cells.

PARK7's Significant Impact on Cell Proliferation, Migration/Invasiveness in Lung Adenocarcinoma Cells

To further verify the PARK7's potential related to metastasis-associated functions and service as a biological marker, in the present example, the A549 cells were additionally employed for test. As shown in FIG. 5, first, CL1-5, A549 and CL1-0 cells were treated with PARK1 siRNA respectively. The siRNA of PARK7 was purchased from Santa Cruz Biotechnology (Santa Cruz, Calif., USA). The sequence of the siRNA was the sc-37080A sense: CUCCACUUGUUCU-35 UAAAGATT (SEQ ID NO: 3) and antisense: UCUUJAA-GAACAAAGUGGAGTT (SEQ ID NO: 4), sc-37080B sense: CGACGAUCACUUAAGAGAAATT (SEQ ID NO: 5), and antisense: UUUCUCUAAGUGAUCGUUCGTT (SEQ ID NO: 6), sc-37080C sense: GGAAGUAUGGAAGUCA-40 CAATT (SEQ ID NO: 7), and antisense sc-37080C:UU-UUGACUUCAUACUUCCTT (SEQ ID NO: 8), and compared against scrambled siRNA which served as the control. As shown in FIG. 5A, first, the level of the PARK7 protein expression in the cell lines having plasmids treated with 45 PARK7 siRNA or transfected with PARK7 DNA was confirmed, to ensure that siRNA successfully inhibits PARK7 performance in the cells, or the level of the PARK7 protein expression was increased due to the plasmids transfected with PARK7 DNA.

The results of MTT assay indicated that with the reduced synthesis and secretion of PARK7 in CL1-5 (FIG. 5B) and A549 (FIG. 5C), cell proliferation was significantly reduced.

According to the results of MTT assay, the proliferation of CL1-0 treated with PARK7 siRNA was also influenced and 55 was reduced slightly (FIG. 5D). Further, CL1-0 was transfected respectively into empty plasmids (control group) and plasmids carrying PARK7 DNA. The results of MTT assay shown that CL1-0 cell transfected with the plasmids carrying PARK7 DNA CL1-0 grew better compared to the control (FIG. 5E).

In addition, FIG. 5F shown that the migration of CL1-5 and A549 cell lines were greatly reduced due to the treatment with PARK7 siRNA. In the case of lowly invasive CL1-0, it was also found that the cell growth and migration were reduced 65 when the expression of PARK7 protein decreased. Conversely, the growth and migration of lowly invasive CL1-0 cell line were promoted when PARK7 was over-expressed.

Clinical Expression of PARK7 in Tissue Specimen and Plasma

Next, the clinical expression of PARK7 was confirmed by tissue specimen and plasma. The tissue microarray including 64 cancerous tissues and 31 adjacent normal tissues was used. By international standards, the number of the cancer diagnosis phases is defined in terms of the TNM system embodying different notations including the tumor size (T), regional Lymph Nodes (N), distant Metastasis (M), wherein the level of the PARK7 expression had a high degree of correlation with TNM stage and lymph node metastasis. In addition, as shown in FIG. 6A, the levels of the PARK7 expression in cancerous tissues were significantly higher than that in nor-

mal tissues. According to the result of receiver operating characteristic (ROC) curve analysis, the stage I and stage II of the patients were distinguished clearly by the different levels of the PARK7 expression (FIG. 6B). In clinical expression, 5 PARK7 levels within the plasma samples were significantly higher than that in the normal tissue. According to the Kaplan-Meier of FIGS. 6C and 6D, when the cut-off value of PARK7's expression level was within the first quartile, patients with levels within this quartile had 3-year survival 10 and progression-free rates; however, when the cut-off value was below the first quartile, patients with such a level had lower survival rates than patients with levels above this quartile.

SEQUENCE LISTING

```

<160> NUMBER OF SEQ ID NOS: 8

<210> SEQ ID NO 1
<211> LENGTH: 31215
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

ccgaaagtgg acctacgtca tgcaggtaag tcggtaggtt tccggcgccc agcgccccgt      60
gggagttgtc tctggtgcc cacgctgggg gggggcttcc cacactggtg ggccgcagagg      120
cgaagccgtt cccaggggccc ctcacagaac tcggtgtcag aattcccccc cttgcaccag      180
cgccgcctca aatgtcaggg ctgcggccact cttctccggt ctgcggcaca taaccttttg      240
ggggctccag aggggaaatt tgccgtttct gccggaccgc tctagagcgt gcctgaaccc      300
ggccttatg ggtatgttgc acgtacgtt attcagtgc ccagaggcct tctttatgcc      360
cagtaactac aattnaaatt ctttctcgc ttcatgttgc agtcgtctgg tgaatttgc      420
gtgagaaata agattnaaat aggaataaga aatttagtga aatcacattg tagagttctg      480
caaatgtaaa atattnaaatt atagcaataa agcaggcgtt caaataacag aggatgaaag      540
caggataata ctggtcaga acctgctgta tgccaggggc tgtgacagat gctggggatt      600
cagcaaccac caagacaaga aggttctcc ggcgttcaca ggactagggg aagacacaat      660
aaataactaa aggcaaaatg ctagaatgtat ggcgtctc tcaagatgaa atatagaaca      720
tgattnattt tttattnnta tttattnnta ttttgagacg gagtttcgtt cttgttgc      780
aggctggagt gcaatggtgc gatcttaggtt cactgttacc tccgttccc gggttcaagg      840
gatttccctg cttcagcctc ccgaaagttag ctgggattac aggtgctcgtc cactacgccc      900
ggctaatttt tttgtatntt tagtagagac agggttcccat gatgttggcc aggggtggct      960
ggaactccata acctcagggtt atccacccgc ctccgttccc caaagtgcgtt ggattacagg      1020
tgtgagccac tgcgcccaggc cgagaacgtt ttattnnta gtgttactt aatgagatgc      1080
ctaatgtaaag agtgaccat gaaaaataaa taacttggca gcagttttt ttggccctaa      1140
gatcaggaca attctgaggg gagttttttt ttggaaacgtt gaccagatgg ccatgggtgg      1200
ctattactaa cactgtcaat gccatttctc ttttatttgc ttgtgacccctc cacaggcaga      1260
gcaatatttc atcattaaaaa gttgcaactg ctatgagaag ctacgttccct tgaaaacaga      1320
gtttttggcc aggaatagtt gcttatgcct gtatgtccag ctacttggga ggctgaggca      1380
ggaggatccc ttaagcccgag gaggtggagg ccaacactggg caacatagcc aggcccggtc      1440
tctaaaaatg aaataaaaacc ggcagtttct tccttgcgtt ctcccgactt gcataaaagag      1500
ttgtcaatg ttgagttaaa aaggttagtgg ataggatggg gcggttctgc ctggaaattg      1560

```

-continued

gagactgaac taggaagtgt cttcggttc agtactacag cagttttt tggtaatgg 1620
tttaatttt tggtttatc ttatgaatgt gtgtatgagaa atatgcata actataggt 1680
gtcttaatgt taactgactt ttaatattga cagtatattgg tgggttaggt gtgaaattta 1740
geatcagaaa tctgaatttg accaagactg caggaccctt tacagtcatt tcacccttct 1800
ggacctcaac cttcacatcc gtggaaggaa aattgtaaaca cctgccagga agtcaatata 1860
taagggtctaa agatgataaaa tgagaataaa aatattagca tactgttca aaatactgtat 1920
acactaccag aagaacacgt tgaaagaggt gaaaatactt gttctgggg agcaggggctg 1980
aggggaagga ctgagttaga gggctgctgc tgcatggatt cactactgtct ctgtagcaaa 2040
acctggctgc tacagttcac cggtgggtt tagtaactct gttcagggtt gtttagttgtg 2100
cagggtggct agggccgcctc tggtccacat gttcattctg aaacccaggt tgagggaaca 2160
gcagcaactt gcctggggaa aaagctttc ctacagaat taaaaagtag aagagcacaa 2220
ctaataatc agggcagact tttcaaggct ttgttacagg tgcattttaa cattccatgg 2280
accaaaaacaa ggccaaacccc aaaatcaagg gacaggaagt agactccacc catgcagggt 2340
gaaggggagt gactattttc gaaaataat ccaatctgc gcaagtaata cttgactttt 2400
taaaactgtg cagtgatattc acttgtaag aattaatgtt gactgtggc catttcagggt 2460
cttgatggt atgcgtatgt ctcaggaatg ttaactccatg ttcatctct ctggctctca 2520
ctgctgaaac atctgtcatc tttaggctat cgtggctgtc tcatgtgtat gcagaccagg 2580
agcaggagca ttgggtactc cttttaggag ttaccacgg ggccgggct cgggtggctca 2640
cgcattgtat cccagcactt tggaggccg aggctggtagt atcaacttgag gtcaggagtt 2700
tgagaccagg ctgaccaaca tggtaaaacc ctgtctctac taaaacaca gaaaatttag 2760
ctggcgtgg tggtgottgc ctgttaaccc agtactcag gagtctgagg cagggaaatc 2820
acttgaaccc cggaggcaga ggttcagtg agtcaagatc atgccccac actccagct 2880
gggtgacaga gagactcaaa aaaaagttt accacgcaga ctggatcaaa aaagctgtc 2940
ttcttttgtt tttccctcca tctactgtt tccctcttgc gttctagaag cacacatctg 3000
accacttgc tttccctttt ctctgtcatc cctgtttcc acactcttc acagctgttt 3060
ccttgcataa tagccaaag tgaagtcatt ccagaactcc taaaagttt ttcttaatgt 3120
tcatatgatt aaagacattt cagactttt cacaaggatca gtgttcatca attattcaca 3180
tttttttttt ttttttttag agacacagtc tcaactctgtc atccagctg gagtgcagtg 3240
gcatgagatc atgacccact gcagccttgc ctcctggc tcaagtgtt ccccgctgc 3300
gtgtcagcc tctcaagtag ctgggaccca taggcgtgtt atttttaaa ttttttttag 3360
agacagggtc ttgcatgtt gtccaggctg gtcccaact cctgggtca aacaatccctc 3420
ccgcctcggc ctcccaaggt gttggatgtt gacacccgc acagctccaa tttttaaaat 3480
taataaaaat aacacactca ccatcattgtt aagaatcaca taaaatatac caaatgtctt 3540
tgttaactaa caaaaaattt atttcttgcataa ataaatgtgg ccaggtgcag tggctcacaa 3600
ctgtatcccc agcaacttgg gaggccgagg tggcagatc acttgcggatc aggagttgt 3660
gaccagtttgc gccaacatgg tggaaaccccg tctctaataa aaataaaaa attagttggg 3720
catgtatggc cagcctgttgc tccctgttgc tccggagac tgaggtacgtt gatattgtt 3780
aacctggag acagaggatgttgc cagtgagccg agatggtgc actacacgccc agcctggatg 3840
acagagcaag actctgtctc aaaacaaaaa caaaaaacaaa acaaagaaaa taaaatgtat 3900
tttttttttt tttttttagtcc aagagtctcg ctctgttacc caggctggag tggatgtgg 3960

-continued

cgcatctcagc tcacttcagc ctccgcctcc cagggtcaag caattcccct gcttcagcct	4020
ccccgagataat tgggactaca ggtgcaagcc accatgcccga gctaattttt gtatTTTtag	4080
tagagaccgg gtttcaccat gttggccagg atggctcga tctcttgacc tcgtgatctg	4140
cccacccctgg cctcccaaag tgctgggatt acaggcacgc accaccgcgc ctggccagaa	4200
acgcgatttt aatatctaaa ttgaaacctt aaaaacactg atgtatTTtag gccaggtgct	4260
gtggctcaca cctgtaatcc cagcactgtg ggaggccgag gtgggcagat cacttgaggt	4320
caggagttt agactagcct ggccaacatg gtgaaagctc atctctacta aaaatacaa	4380
aatttagccag gcatgatggc aggtgcctgc aatcccagct actctagagg ctgaggtggg	4440
agaattgctt gaacctggga ggccggagggtt gcaatgagct gagattgcac cattgcactc	4500
cagcctgggc aacagagcga gactctgtct caaaaaaaaaaaaaaaaagaa aagaaaaagaa	4560
attactagaa gaaaacactg ggggggggggg ggccaggcact ggtggctcac acctgtatc	4620
ccagcacttt gggaggctga ggcaagtggta tcacctgagg tttaggagttc gagaccagcc	4680
tggaaacat ggtgaatccc tgcgtggact aaaatacaa aatttagacag gcatgatgga	4740
gggtgectgt aatcccagat actcgggagg ctgagacaga gaatcgctt aacccaggag	4800
acagtggttt cagtgagccca agattgcgc actgcactcc agcctaggcg gctgagcgag	4860
actccatctc caaaaaaaaaaaaaaaaagaa agaaaagaaa gaaaacactg gggaaatgtt	4920
ccagggattt gatctggca aagacctcaa agcacagaca acaaaagcaa aaacagacaa	4980
atggaaatttcc atcaaactaa aaagtatatg cacagcaag gaaacaacaa agcaaagaga	5040
caacacacag aatggagaa aatatttgc aactatccat ttgatgaggg actaatgact	5100
agaatatattt aggagactaa tagcaagaaa acaatcagat ttAAAAGTGG gcaaaagatc	5160
tgaatagaca tttctgaaga gatacaaatg gccaagagat atgaaaaagg gctcaatgtc	5220
actaatcaga gaaatgcaaa taaagacagt aagatatcat ctcatccag ttAAAATGGC	5280
cttttatcaa aaggaaataa catgctgaga tggatgtgaa gaaggaacct catacaCTGT	5340
tggcgagcat ctcaattagt gcagccacta tggaaaacaa tatggatcc tcagaagatt	5400
aacttctgag aaatcataag ttctggatc ataactacca tatgtatccag caatcccact	5460
accggatat accaaaaaaga aaggaaggc caggcacggg agctcacGCC tataatccca	5520
gcactttggg aggccgaggc aggcagatca ctgggggtca ggagttcaag accagcctgg	5580
ccaaacatagt aaaacccctgt ctctactaa aataaaaaaa ttagccaggc atggggcac	5640
acacctgttag tctcagctac tcgaaagact gaggcacgag aattgtttca acacagaggc	5700
agaggTTGCA gtgagccaaatg atgggtccac tgcacttcag gctaggcgac agagcaagat	5760
ggaggtctcaa aaaaaaaaaaaa aaagaaagaa aatcaatata tcaaagagat atttgactc	5820
ctatgcttat tgcgtactg ttccacaacag tcaaaatatg gaatcaacca aaatgttcat	5880
caatggatga ctggataaat aaaatgtaaa tatacacaat gaatactatt cagccataaa	5940
aaataataaa atcctatTTG caacaacatt gatggactg gaggtcatTA tggtaagtga	6000
aacaagccag gcaaaagaaag acaagcatca catgattca ctcatataatg ggaagttgaa	6060
aagtggatat catgaagata agttgggtgt taccagaggc caggaagggt agccaggaga	6120
aggggatgaa cagggtgatt aataggtaca aaaattggta gaagtgcTGG gcaaggtgtc	6180
aagagccccca gcatcagaaa gtggtcgact tgctggTTGG taagaagaat ttatcgacaa	6240
caatataggT ttgaaaaagg aaagttttat tagaacgctg cagaagagtg cagcctcagc	6300

-continued

aagagagaac tgagcatgcc gcgggtggatt tttcatgtcc ctttcaaat gtctcattt	6360
ttgcaaattc aatccaagtt gcgttcattt agccaggatc cttctaagct cattcaagaa	6420
tttgggctt taactattt ctttgattt acctggtacc aggtgecaac tttgataat	6480
agggatatct aattacttct aaattcctca gataaggggc ctgcttgatg gtcaccagg	6540
gatctgtgtc tccttaaga gggataaga cctagcggt gcagagtct gtaggggtac	6600
tatagttaac agtaatctgt tgtatatttt aaaatgttat tattgaagag agtaactgga	6660
atgttcccag tataaagaca aatgtttaag gtgatagaga tctcatttac cctgattaa	6720
tcattacaca ttatatgaaa gtatcaaatt accacatgtc cccagaaaac acatacgtct	6780
cttacatatac aataaataca acttgagatt atgatgtaaa tacatctgac caacttggta	6840
ctttagac ttatgtgcgc agcactgctc tagtcctgtc ggtgcagcag catcaggatc	6900
gttaaagaaa acaaacaatg ctgagaaaaa aactcacacc cctgagacat ccgggtgtga	6960
ataaaatgcgg cagactcgcc cgagatcggg agaccaggcg tgggggagag gtccgggagg	7020
cctggaccag agtcctaaca gaccagaggc gaaacgggaa ggcgcgcag aaaaggaca	7080
acgcaaaggg agcaggcgtc cacggagcgc gaaactagga accccctctga caaccccagt	7140
ccctcggcag ttccagagac cggctcctca cggagggtgg cggtagagac tgttaagccc	7200
cgcggggcgc gggcaggcc ggactgtgcc attcgtgggg ggtaccatgt gggaccgagc	7260
cgcctcacc cggctgtcc agctagaaac tccccgtgc caaaaaaaaa tcagtcggag	7320
gtagactcgg cccggacgtga cgcacgtga ggccaaaggcg gcgttagtct ggcacgtgt	7380
gggctgaggg aggccggacg ggcgcgtgc gtgctggcgt gcgttcattt tcagcctgg	7440
gtggggtgag tggtaaaaaa cggggccgggg cggccgtcgc gcaggaagag ggcgggggt	7500
caggctcagcg ccaggggggg cggccgcgcgt gtgtggccg tggcgctgg cggcggtgg	7560
gtgctggacg gtgtccctgt gctggacggt gtcccgctgg ctcagaaccg ggcggggcc	7620
tgggtcgcccc cggccctcgc ttccggccctc ccagtcggcc cctgtcgctg gcgttggatt	7680
tgactgaccg ccagcgtggt ggcaacgcgt aagcgtccag aatcttctgc ctaacctctc	7740
gcggccatgg aactggctag ccgttttatt aaactctgtt ttgcgtggac ggtaaaccct	7800
ccagataatc tgtaaatagg ctaaaaaaaaaa ttccggaaacct cgtttagctg ctgtcggt	7860
cagtgagaac tccgcgcaga gagacagatg tagttgggtt gacttcagtg aggggatttc	7920
catcttctc agtcattaaa aaaatgttcc agacattaa cactgttgc ccccacacac	7980
aattttttag tacagtata actaagaaaa caaaaatccc ctccaaaaaa ttacaagtt	8040
attgcgaaag accacattta aattttgcc catgaaattc agtttagtgc tttctctgaa	8100
acagtgttcc aaaaagact gttccccgc attgtgtgaa atgcaggaga cccacgtact	8160
tgtatTTTA aaaaacccat ttgcaacata ctattaaagt tggatttaag agaacatgg	8220
agaagaaaaat ctaagcaata ctacacctt tagcaccctc attatgtttt catctcagag	8280
caattaaaac tgctatacaa atcaacgtta agataactaa actgctgtt ttttgtt	8340
cagttgtcta tgaaaaaccgt ttcccttagga agtacttact ctgcttgaaa atgctctaa	8400
actttaaatt ttggggtatac tcagggttgc aatgaaagt ttttgaatc ttttttttt	8460
ttttttttta aggcttgtaa acatataaca taaaaatggc ttccaaaaga gctctggta	8520
tcctggatca aggacagag gaaatggaga cggtcattcc tgcgtatgtc atgaggcgag	8580
ctggggtaag tcccacatcg attttagcc attcctgttt taaatgtttt tggattttt	8640
aatcattttt aataaaatat tcaaagtgtc ctatgaaata tttcaaatac acacaaaatt	8700

-continued

tcagagatga cataagaata aatacctgtt gatccactgc tcacattaa cgcttgtaa 8760
 tgtcttgcca tatttccttc agacccttt ctctttgtt ttgagctctg tcgtccaggc 8820
 tggagtgcga tggcaggatc ttggctcatt tcggctctg cctcctggc ccaaaccatc 8880
 tccccacctc agcctccaa atagctgaga ctacagatgc gtgccaccac acctggctaa 8940
 ttttgtatg tttttagag acagggtttt gccatgttc ccaggctgct ctccaactcc 9000
 tgagctcaag ttgtccaccc gcctcaggcc tcccaaagtg ttaggactac aggctgagc 9060
 cactgcactg tccttagacc catttctttt ttcttctttt ttttttttt tgagatggtg 9120
 tctctctgtg tcgctcagcc tggAACGAG tgggtgtatc tctgctcgct gcaacctctg 9180
 cctccgggt tcaagagatt ctccgcctc accctcagct gggattacag gtgtccgcca 9240
 ccacgcggc otaattgtat ttttagtaca gatgggtttt caccatgtg gccaggttgg 9300
 tctcgaactc ctggcttcaa gtgacccggc cgccttagcc ttttacagtg ctgggattac 9360
 aggcaggagc caccatgccc ggcccccctag actcgttct taaagagcag atgcttcaaa 9420
 gaaatacatt tgaagccccc tttgtaaatt tctccaatcc tatgcccctt cttcccttct 9480
 taaagataag tgctatcctc gcactcttgt gtatccatgc atgtgtgtct ttttttttt 9540
 ttttaagaca gagttttgtct ctgtcaccca ggctggagtg cagtgggtg acctcagctc 9600
 actgcaacctt ctgcctcctg ggttcaagca gttctctgc tcagccccc aagtagctgg 9660
 gattacaggt ggcaccacc accatggct aatttttgtt attttttagta gatgggtttt 9720
 caccatcttgc cccaggctgg tcttgcactc ttgacccctg gatccaccac cctccggctc 9780
 ccaaagtgtt gtgattacag atgtgagcta ctgcacccgc ccccaegcat gtcttaagg 9840
 tagcatttgc ccgtggttct cattttgcgt gtttatatat tatctctctc tatctaaaaaa 9900
 tagtgaacag tgaagtgaag tagaactaac tctgtgccag gcagcattct aagtgcgcgt 9960
 aaacccatataca acaatgtcgat gagttagata tcaccatcc cattttacag ttgaagaaac 10020
 tgaggcacag agacataat aatgtacca catcacgtat taagtacaaa agccagaact 10080
 cagacccagg cagccctggcc ccagactctg ttaaccctat actccctctgg ttctcagaaa 10140
 tgaagataca tgcgttattaa gtttatccac ttAAAATTGC tgcttgggtgt tgactgaat 10200
 gcccacatct acccatttcc ttaatttacag cattacaatt ctgtatatacg tattttgtg 10260
 taggtttctt tgcgttatttgc tggaaattttccatgggtt atatatctaa aagttagatg 10320
 actaggccga agatagccct gtatcgca tgacttaggtt ttgccaagg gctctccagt 10380
 gtcccaagg ttagtccac cagcagtgtat gggaaattcc cactttccca gtgcctcgtc 10440
 ttgggtattgt tgactttaaa aattttgaa agataaaagca gtatccgtt gtttggactt 10500
 gcatatctat ttacaaaaaa taccatgggg tttaaatggc aacagtaaac ttgcaagatg 10560
 agtttataat aggtatgtca tataactgtt cacccaaacc agaacatttg tgggagaaag 10620
 ggtgttccag tcccacagag tacaggccag cagctataag tagggctgtt cccggggcaaa 10680
 ccagggtaga octagttattt aaatataattt agccagtgtat ttagctaaa tttggatag 10740
 ttgtggcgtat tttttccatc tcatgttact ttcaaaacaca gggcagctgt gtaaaacgtt 10800
 ctcttagctgg gtgtggtggc tcatgtctgtt aatccctcgtt acctggagg ctgaaggcagg 10860
 aggtatctt gagcccaagg gctggaggctt gcagtaagctt atgattgtgtt cactgcctc 10920
 tagcccaagg ttaggggtga gacccatct ctcttttttca aagacagtgt 10980
 tactctgaat ttatgtttca gtgttcttaa atatgataac atctttctcg tagattaagg 11040

-continued

tcaccgttgc aggccctggct gaaaaagacc cagtacagtg tagccgtat gtggtcatt 11100
 gtcctgatgc cagcctgaa gatgaaaaa aagaggttt taatccatac atggaggat 11160
 tccttcataat ggcttcttg tttcttggaa tgtcttaaga gtgtttag cacagactca 11220
 ttttagaaaa ttatggct tgaatgtctt cccctgacag attaagaggg tgaggactt 11280
 gtctttctat tctgtatctg tagaatgtgg caattgtttg atacagaatg tgcttagtaa 11340
 gtgggtggct ggatgggtag gtggccgggt ggatgtgtgg ccagatgggt gggttggc 11400
 ttagatggat ggctgcattt tttccatc agtattttc tggcttacac aggcatcctt 11460
 gcctcctatt acacatttt acctgacata aatcaactgc cacatccc attttttatt 11520
 attattat ttgttagag gaatggtccc actctctccc ctaggttgg gtccagtgg 11580
 gcagtcacag ctcaactgcag cctcaaccc ccaggttcaa gcaatccccc cacctcaacc 11640
 cccccacgtag ctggactac aggcattgtgc catgccccgc cattatccc tctaaagata 11700
 cttagttagt tccactgttag ttgttgtt tttcagat cgttggaaatt atggcttta 11760
 ccttaagga cgatggacac ttttggaaagc tagcatccct tccctcagaa acatgtccc 11820
 ccacaggcgc ttttgcacac tccgtcggtgc ggtcagcgtg acaggagtgt ggactgtacc 11880
 ctctgacagc agggtcatgg cagggaaagga ggcagagtcg gtcacagat ggctgggtgc 11940
 acactgtga ggaaccttggc gtgcgggtcc ctggggccgag ctgtcctcag atacatagga 12000
 aaaagtttaa tccttctaa taagtttaga ttttcttta ctggatttggta gaaaatttaga 12060
 ctgttgtat ttacatgtga ttgttgttggaa caaaataaaa atgacaagca gaagtaagta 12120
 ttccaggcca agtgcgttgg ctcacctgtat atcccagcac ttttggaggc caaagtgg 12180
 ggatcaacttgg gggccaggag tttgagacca gcctggccaa catagcgaga ccgttctct 12240
 ttaaattaaa aattttgtaaa agccagggtgt ggtgggtcat gcctgttagt cttagtactt 12300
 aagaggctga ggcaagagga tcacttgacg ctagacgggt gcttggccca aggaatttga 12360
 gacacgttgc aactgtgttgc gtgcattgc ctttcagccct gggtgacaga gcgagaccc 12420
 gtctcaaaaa taataataat acttttttc atctctgttt gtgttttgtt catatgtat 12480
 ctgggcattt taaaacagtgtt gttaccttta tttcaatcg acagataata agtgcata 12540
 ttcatggat ttgtgtatgtt tccatgcata atatatagtt atcggatcag agtaatttgc 12600
 atatccatca tctcaaacat ttctttgtgt tggaaacgtt caatatccctc cttgtat 12660
 gaaactatata atgattgtta actatagtca ttctacgggg gtatagaaca ccagaaccta 12720
 ttccctctat ctatgtataa ttttgtatct tttacaatctt ctctccctat ccccaacttc 12780
 tccatccctc cccagcccttctt agtacccctt gtcctacattt atgttctat gtgtcaatt 12840
 ttttttttagt tttcacatata ggttggaaac atggagtgtt taatggctt ttcctggctt 12900
 ctttcaacttata atataatgtt ctcttagttcc attcttgcattt ccacaaatgtt caagatttca 12960
 ttctttttta tggctggata gtatcccattt gtgtataat ggcacatttt ctttatgcatt 13020
 tcacatgttgc ttggacccatg gtgttggctt agtgtgactt ttgttgtat 13080
 aaacaagggtt gtcagggtgt ctcttcgtt tactgatttcc ctttccatgtt gatacatgcc 13140
 aagttagtggg attgtggac catatgttag ttccattttac tttttttttaaaggtt 13200
 gttacccatgtt gtgtgtttt attttcaatgtt gcaatgttca aaagggtttaa aataaatttca 13260
 atactttataa cattttcttt tgatgtttgtt gctttgttgc gtttggatc aacggtagga 13320
 tggtttatgtt cttaaaatgtt attcttaagcc agccatgtt gttcacaccc gaaatccat 13380
 cactttgttgc ggctggggca ggaggatttac ctgagcccaag gagttttggacttgc 13440

-continued

gcaatgaagc gagaccctgt ctctacaaaa ataaaaaaaaa ttagctggct gtggtggtgc 13500
 atgcctgttag tccttagtcc tgcatgggct gaagtgggg agttgttga gcccaggagt 13560
 tcaagggtgt agtgagccac gattgcatca ctgcactcta gcctgggtga cagaggtgag 13620
 ggcttcctc taaaaaaaaaatt ttatagggtt cactaaatac ataatacatt tttatTTTGT 13680
 aattttgttta atgactagat ttttttaac cacttttaa agtactaaag tattgttgc 13740
 cggccacagt ggttcacgccc tgataatccca gcactttggg aggccgagat ggggttatca 13800
 cgagggtcagg agtttgagac cagccctggtc aagagggtga aacccatct ttactaaaaa 13860
 tacacagatt agccgggcac agtgggtgggt acctgtatcc ccagttgtt gggaggctga 13920
 ggcaggagaa tcgcttgaat ccgggagacg gaagttgcag tgagctgaga tcactgcact 13980
 ctaacctggg tgacagagca agactctgtc tcaaaaaaaaaa aaaaaaaaaaaga aaagaaaaat 14040
 aaataaaataa ataaaaagtc cttaagtatt gttaaaacaa tttccgtttt gtaatttcag 14100
 gaagtttgaa attaatttga ttcttaggtat tttttggggg ggataactaaa attctcccc 14160
 cgttacattt ttcataaagt taagaaaaat tttttgtgcc ttttacttaa aatttggttc 14220
 tctattaatt ttatTTGTT tttagacag agtcttgctc tggtgeccag gctagagtgc 14280
 ggtgggtcag octcagctca ctgcagccctc tgccctcttag gttcaagcga ttctctgccc 14340
 tcaacccccc aagtagatgg gaccacaggt gtgcaccacc acacccagct aattttcata 14400
 ttttttagtag aaatgggggt tttgccatgt tggccaggct ggtctcgaac tcctgagctc 14460
 aggttaatctt cctgccttgg cctcccaaag tgctgggatt acagacatga gccagtgtgc 14520
 ccagcctgtt ttcttattaa ttttttaagt tgttcatgtt cattcttggt gaacaataat 14580
 tcaaacaata tagacacata taaagtcaaa atgttaatgt tctcttctc attctccctc 14640
 tgccccatcc cacactactc ccattagcaa ctagagtgtc ttcccttgc tggactacc 14700
 tgtatacaga atatgtgggg tgggtgtt gttgtgattt tacacataca cgcatacata 14760
 tacacacaaa tacatatatac ctgtctttt acaggaagga gattatacta cccctgcata 14820
 tctgcacggtt ggacatccctt gcatgtcact acatacagggt tttctgcatt ttttgctagt 14880
 taaaacacca ttccgtcatg tggatacacc ttaattttttaactgttctt attggcagat 14940
 aggctatctc ctgtacttcc cacattaaa ataggaaagt attattggac tgcataattta 15000
 atgcacagtt gaaatgaaat gttttgttt tctttatgtt ttaaactgtt acagggacca 15060
 tatgtatgtgg tgggtctacc aggaggtaat ctgggcgcac agaatttatac tgaggtaaaa 15120
 aattctactc aattataacctt caataaagct gggggggggg aaaaactaaa gaatttcagc 15180
 atctgcttat gttctgttaa ttttgttattt attcaaataat ttccggagga ggctgtgaaa 15240
 aaaaaataga aacaactaaa attaacaaaaa tgggttataa gcattaaactc aaacttttt 15300
 ttttttttga gacagagtct tgctctgtgg cccaggctgg agtgcagttgg cacaatctcg 15360
 gtcactgca atctccgcct cctgggttca agcagttctc ctgcctcagc ctctgagtag 15420
 ctgggattgc aggcatgcac ccccatgccc tgctaaatttttataat ttagagacgg 15480
 ggtttccacca tgggtggccag tctggcttca aactcctgac ctgcgtatcc gcccaccccg 15540
 gcctcccaa gtgctggaaat tataaggcgtg agccaccactt cccgacccatca agaaaacatt 15600
 ttaatattt tctatgggg tcaagggtcag tggctcaacg tctataatcc cagtggttgc 15660
 ggaggctgag acaggaggat tgcttgaggc caggagtttgc agaccagcct aagtaacaca 15720
 tcgagacgcc atctctacaa aaaattttct ttaatttagc tgggcacggt ggtgcacact 15780

-continued

tgttagtccca gctactcgaa aggctatggg gggaggatga cttgaggcca gggatttag 15840
 gctgcagtga gctgtgaatg caccactgca ttctagcctg ggcaacaaag caagaacctg 15900
 tcttatcaga aaaaaaaaaat gttgccatgg aagtaagctg aattgggtggg accgttatga 15960
 acagatgtcg atgaatacag tccaaagtaa gatgattgg ttttttcca ccagcagaag 16020
 aatgatcaga ttttgttgg tgagaaggcc aaattgtcta ctcaaagtct taactgggg 16080
 aagctgtggg gctagggctg ccagcaggaa tggcaaatgc catcagcaga gaccattgtt 16140
 cctcatttta agtcgtatgt gaggagtcag aggcacgggt gaggggcaca cctgcaggca 16200
 gagttggggc tgccagaagt aagaagtggg ttgtgtcaga cacaaggat cttttctgc 16260
 tagattctgt tcctctctt gccatctgaa aacacccaaa acaccacatt ccctcccatt 16320
 tctttctccc tggagtacaa aatggcaagg gtcaaattgc ttcttctgtat cttaaatgt 16380
 ggaagagtgcc gtttctctt tgagaaatgc cttgcttggg tttaagaata taatataagac 16440
 acattttgat cattttata ccaatgattt agaaatatttggg ttggaaaata ggtcagag 16500
 cttgtggttt aaactaaaaat taaattcttc caaagttcc tagttagtga ttggtagt 16560
 gcttaatgtat aactttatgt atttttgggtt ttcttttcac tagtctgctg ctgtgaagga 16620
 gatactgaag gagcaggaaa accggaaaggc cctgatagcc gccatctgtg caggtgacgt 16680
 gcaggggcag cctgtgttgc agcgtcatttgc gtgggtgggg tagccttca ttgcgtgg 16740
 tgattccaaa tagctcttcc ctttcataaa gcatgcaggg catctgtgtt ggtgtatTTA 16800
 gtttgggtgg catgaagtttgc gtgtcatttgc agagatgagg acaattgttgc tggtttctgc 16860
 ctctccatgc ctgggtctca catgctgtga aacttagtgc ttccgtgtt tggttgcac 16920
 cggaggaaaa taaggccctc tggaaattcag taaacagctt gttacagcaa gtctctgtc 16980
 cagaaagtct ttgtgcagc acacaatcag caaaatccat caaacatcaa cacagcag 17040
 ctgtccctgtg ctggccctgc aaattcagaa gccccatgg tgcttccgc tggcttc 17100
 ggcgtttctg attgtctcag taccgagtga tcttggcac cgcattatct gccacataat 17160
 ttagaacaag gacatttggt gcttcgcaga tgtcccttc tctttgtacc ttagtaat 17220
 ttatTTTCTC cataaccatt ttaagatcca ttcttgc tttccatca gatgtgtt 17280
 tgccatttttgc ttgggtttcc atgtgtaat ttggccagc accttccttgc ttgtataagg 17340
 cttcattaaa tattttgtcag ggccgggcgc agtggctcac gcctgtatcc ccagcactt 17400
 gggaggctga ggccggcaga tcacactgagg tcaggagttc aagaccagcc tggccaccat 17460
 ggtgaaaccctt catctctact aaaaatacag aaattagccca ggcgtgggtgg cggggcctg 17520
 taatcccagc tactcgggag gctgaggcag gagaatcgct tgaacccggg aggcggaggt 17580
 tgcagtgcgc cgagattgtg ccgttgcact ccagcctggg ggacacgcgc gagacttcgt 17640
 ctcaaaaaaa aaataaaata aaataaaata aatatttgc agaagagtga atgaataaac 17700
 gaatgaatga gtggatgggtt tggtaaacat caacatcaa acatgtgttgc tttgttatTT 17760
 tttcaatac agtaggcttt tcaaaaaggat ttatggccca gaggtctgg ggacttgata 17820
 cattcggatca tcaatgttct tttgggtgcac ttgcaggatca aaagcagatg 17880
 ctactgaggg ggcagggtgtg gtggctcatg cctgtatctt cagcattttgc ggaggccaa 17940
 gcagaaggat ctcttggaaag ccaggagttt gagactaacc ttggcaacat agccagaccc 18000
 ccatctcaac aaacaaacaa acaaaaaattt agccaaagcc acgtactgcat gcatgttagt 18060
 ccagctactc aggaggctga gatggggagga tcgcttgcag gcaagagttt gaggctgcag 18120
 ttagctatgtat ttttttttttgcacttca ggcctgggcag cagagtgcaca ccatgtctt caaacaat 18180

-continued

gttattcgcc tttttcttc tcagtcttc aggagtgaca tcagagtagg atgataccat 18240
 catctgagaa ttttatttgc tgaaaaaaa attccccagt tttatttagt tgatgtaaaa 18300
 gtaattgtgg ttttgccat taaaagtaat tggcgtggca cagtggcgca tgcctgtaat 18360
 ctccacactt tggaaagctg aggtggggcag atcggtttagt gtcaggagtt caaaaccagc 18420
 ctggcaaacg tggtaaaatc ccgtttctac taaaaataca aaagtttagt gggcatggt 18480
 gtgcacgcct gtaatcccag ctactcgga ggctgaggtt ggaggatcac ttgaggtcag 18540
 gagttcgaaa ccacgttgc taacatggt aaaccccgtc tctactaaaa atacaaaagt 18600
 tagctggcga gtttagctggg tatggtgatc cattcctgtat atcccgacta tcaggaggct 18660
 gaggcaggag aatctattga acccgccggg cgagggttgc agtgagccgc gattacgcca 18720
 ctgcactcca gcctgggtga cacagcaaga ctgtctcaa aaaaagtaat aattttaat 18780
 atggcagatg ttcatagata taacccacat aaaagctaaa gggattctaa gacctaata 18840
 tttgagaacc gtggcattag gggctggaa gaaccacaga gtttgaccac cctggcaggt 18900
 cttgtacgtg ggcttactac aagagtccacc actagcctt tgacctgccc tgaggctcag 18960
 gtaattatct ctgccaagg gcactgcgt cactgcgc caagcagctg ctccctctt 19020
 tggagagaaa gtcacagatc cttgagttt gtttctttt gctctgtgc tgtgaagcaa 19080
 gcttcgtcc tagattctt gaccaagga agaaaggtt tggcgtgat ttgtttctt 19140
 atgattctgc taaaagtaaa aaccacatgt cagttgtcc tggccacaa aagtagcaaa 19200
 atcacttaag gtcaggagtt cgaaaccgc ctggccacca tggtaaaacc ccatctctac 19260
 taaaaataca gaaatttagcc aggegtggt ggcgtgcct gtaatccag ctgcttggg 19320
 ggctgaggca ggagaatcgc ttgaaacctgg gaagtggagg ttgcgtgag ccaagattgc 19380
 gccattgcac tccagctgg gcaacaagag taaaactccg tctaaaaaaaaaaa 19440
 aaaataataa aaataaaaaat aacaaaaatt agcagggcat ggtggcgcgc gcctgtcg 19500
 ctagctactt gggaggctga ggcaggagaa tcgcttgcac ccggggaggcg gagattgcag 19560
 tgagccgaga tcgtgcact gcactccgc ctgagcgcaca gagcaagact tcgttcaaa 19620
 aaaaaaaaaaaa aaaaatcaac cacatttgc ttactgtttt gtcgtgaggc tagatggaa 19680
 gccatgtaa gaagcatggg ctttatagta cttaatca acataaaaaa ataaacaggc 19740
 tggctgtggt ggctcatagc tggatccata gcactttggg agactgaggt gggaggatca 19800
 ctgtgaacccca ggagttcaag accaggctgg gcaacatagt gagaccccccc caccgac 19860
 taaaaaaaaaaa tattttaaaaa aatcagcctg gtgtgggtt gcacacttgt agtccagct 19920
 actcaggagg ctgagggtggg aggtactt tgagccagg aattttaggt tacattgaga 19980
 tgggtgtatc acaccactgc acttgagctt aaaggacaga gcaagacttgc gtcttttttt 20040
 aaaaaaaaaaaa aaaaataggc caagggcggt ggctcacacc tggatccca gcactttggg 20100
 aggccgaggc gtgcggatca caaggtcagg agatcgagac catcctggct aacacgggt 20160
 aaccctgtct ctcctaaaaat tacaatggc tagccaggcg tgggggggg tgcctgtat 20220
 ccacgtactt cggggggctg aggccggaga atgggtgtgaa ctgggggggc agagttgc 20280
 gtgagccgag attgcggccac tgctctccag cttggcgac agagtggagac tccatctca 20340
 aaaaaaaaaaaa attatataaa aaacagtaaa aatagaaaaac acactagcag tgggtttata 20400
 ccattgaata tcctgcacca ctgttgggg cactacacca gaaataggaa aaaatgtgat 20460
 gatgagctga gctaatttgc atgagggtt tggaaatggg acagaggagt gatggaaagag 20520

-continued

atttggatct tttaaattgg caaacagaaa aataagattc tttttttttt ttttttttgt 20580
 taaaaatggga gctttgtct tgttgccaa gctggagtgc agtggtgcaa ttccggctca 20640
 ctgcaacctc cacctccag gttcaagega ttctcctgcc tcaggetccc gagtagctag 20700
 aattacaggc acctgcacc accgcaggctg gtctcgact cctgatctcg tgatccgccc accttggcct 20820
 cccaaagtgc taggattaca ggctgagacc accgcaccca gccaagattha ttctgaagt 20880
 ttgcagttag ggattggaaa catttgaac acaaagaata ttagcctagt ccttaatatt 20940
 gagtgaatga ggaacgcaaa ttggaaggga gtctatgtt agaagaaaat taaatgat 21000
 ttactttgag taggggaggg ggaggaagtg tggagttgga ggagtggaca gttgtcagct 21060
 gagatgccc ggtctaggaa tgaggcctct ggaagcaagg tcttggccac ctggaggagc 21120
 tggggagttg gcagaggtgg tcattttgca tgttaccaca gggtggtgct gttggctgca 21180
 gaaggggaca tggtcagctg cgccctctgc actgttagtgc agagtacaga gcgtttcat 21240
 ccatcagaat cccaggctt gggagagtga aacgtctctt ctccagtatt ccaaataggg 21300
 ttctgacgcc ccagaaagca gtgattatga gcttacactga taagtatgaa agacatcagt 21360
 aaattcctga atccaaactgt aacataaatt tattcacatc gtacgtgtga ttttattacc 21420
 accttgaagg gaggcgccta aaaattctcg ttcaccgatc actttcctca ctgtgctatc 21480
 atctattaaa gtttacttta aatgcaga tgatgttaga atttctttaa aaattcttac 21540
 ccaaataaaaaa taaaaaaca tttataaattt cattcaataa aaaattgata attattcaat 21600
 tcttacggac ttctaaaatt tgctaccata catagctgtc ttgtgtgtaa aaataacgt 21660
 gagaagagac atttgaggct tttgatttaa gagctataaa tcaggacttg gtctgaaact 21720
 gacagctgat attaggcaga aagcttatgt aat taggttag tattttgtgt atcttcctgt 21780
 ttgttaacagc tacggctctga gtacgtgtg ggtatattataa ataaattccctt ccttggagtc 21840
 ttgttggaaa atgaaaggac agtaagacca agacctctca ggtttgctga cactaaaagt 21900
 gtacaaactg tgccacagga tcttagccat ccagggcacc ttaagtgtt ccaagatcaa 21960
 ggtgctgttc tgaaacgtat ccttctaagt gtcatgtgag gccttagaaa gaatgtttat 22020
 atgtgtggct tagaggaaaaa aggttagatg aatactttgt aaaaagctt aagatgaaat 22080
 aacaatgaaa ggtatataaa atctttgttt ttaatccctt ttttaggacca ttacatacgc 22140
 aatatgcttg tgaccctccc tgaagttggc cgttttcagt gaatacattt aaataaaaaat 22200
 ctcaagtttgc gacccgtccaa tttggaaaga cttagccatc tgacacttcc atgtggttct 22260
 ttgcttaagt agcttcatc acgtgtatgtc agtgccttta tatctcacac ttccaggcac 22320
 ttcacaggct atctccctca aggacagtgt gctgtccatt ttaatccctac cacctggcat 22380
 acttgggtgg ataggtggat gaacgagtgt taatttccca ttttatttttta 22440
 ttatatttta gacagagtct cgcgtctgtcg cccaggctgg agtgcgttgg cacgttttg 22500
 gctcaactgaa agctctgcct cccgggtca ccccatctc ctgcctcagc ctccccagta 22560
 gctggacta caggcgcccc ccaccacgc cagctaattt tttgtatttt tagtagagac 22620
 aggggtccag cgtgttagcc aggtggctc tgatctctgc acctcatgtat ccagccgcct 22680
 tggcctccca aagtgtggg aatacaggca tgagccaccc tgccggcct aatttcccat 22740
 ttcaagtag aaaataagat tacaaaagag caataaaaatc cagaagttca gagagtacca 22800
 gttgccttta gcatgtactt aatctttcc ttttactaag agtgggtttaa gaagttgagc 22860
 ccggccccaggt gatccctcccc ctcccttggc ctccctggat atgtggtccc tggctgggg 22920

-continued

atgggaaagg tgagagaggt gaggcacattt tgtttatctg tgcgtatctc gctggtatca 22980
aggttaaatct ctgttagtaa atgggttattt aagtatTTT agtttctgtg cttttgccag 23040
atgtgctcag caaatcgTTT gttataaaca tactttatct ctcataactag gaagtgttc 23100
atTCAGAAAT cgttagctgta tgTTTggtaa gaggccttgc atTTTgaaga atactttgct 23160
gttgcagttt ttgttgttgc tagagaaggg gtctgtgttgc cccaggctga tgTTGAATT 23220
ctggggctcaa gcaatTTTc tacctaggcc tcccccaattt ctgggattac aggcattgagc 23280
cactgtgcca ggcactattt cgatTTTTa aacatgggttgc ttctatatac tgcaCTTAgA 23340
ttttttattt ttatttctta ggTCTACTG ctctgttggc tcattgaaataa ggTTTGGAA 23400
gtaaagttac aacacaccct cttgtctaaag acaaaatgtt gaatggaggt aagtatatgc 23460
ttgtttttgt ttgtttgtt gtttttttagt atggagtctc gctccatcgc ccaggctgga 23520
gtgcagtggc gtgatcttgg cttaactgcaa tccctgcctc cggggTTCAA gcgatttttc 23580
tctctcagcc tccTGTAGTAG ctgggattac aggcgcattgc catcacaccc agctaatttt 23640
tgtaTTTTTA gttagagatgg agtttccatca tgTTTggTca gctggatc aactttttt 23700
ttttttttttt tttttttttt ttttgagaca gagtctcgct ctgttgocca ggctggagtg 23760
ccatggtgcg ttctctgctc actgcaactt ccgcctcccg ggTTCAAGTG attctctgc 23820
ctcagecTCC ttagtagctg ggatcacagg tgcgtccac caccgcctggc taatTTTGT 23880
atTTTTAGT agagatgggg tttctccatg ttggcatgc tggtcttggaa cttctgacct 23940
tgcgtatccac ccgcctcage ctctgaaagt gctgggattt caggcatgag ccacccgcgc 24000
cagtctcgaa ctcttgacct tgcgtatctgc ctgcctcage ctcccagagt gctgggattt 24060
caggTGTGTTAG ccacccgcgc tggcccatat gcctgtgttgg gttttttttt tttttttgt 24120
gatggagtct ctgcgtctgt tgcccaggctt ggaatgcagt ggtgtatct cagctactg 24180
caacccTCCGc ctcccggtt caaggactc tccTGTCTCA gctcccgag tagctggat 24240
tacaggcatg tgccaccaca agtttcttgc agactggca cagtggctc ccgcctgtat 24300
cccaGtactt tggggaggctg aggggggtgg atcgcttgc ccccgagtgc gagaccagcc 24360
tgggcaacat ggttaaactc catctctact aaaaatacaa aaaacattttt ccaggcatgg 24420
tgatgcacac tggtagttgc agctgctcag gaggctgagg tgggatgatc gcttaagcc 24480
tgggaggtca aagctatggt gagctgtat ctcGCCACTG aactccagcc tggaggacaa 24540
agcaagaccc tatcaaaaaa aaaaaaaaaa aaagatTTCT tgcgtacctg tagatTTTA 24600
tctatcacat actcattatc ctTTTTATTt taactaaat gagatctact aatgtattt 24660
ttctgcagct tgTTTTTTT aacttaatgt taatatctta tgTTTatctt taacagcaca 24720
tggtagatttta gatttgctc atcTTTGTta agtacagctg ctgcgttgc gttggatgt 24780
gccccatgtt atgttaacctt ctccTGGGGG tgggcatgaa ggtggTTTc tgTTTGCc 24840
cttggtaaacc atGCCATAAT gatcatcTTTt gaatGCCGCT gtgagcatat ctgagctcca 24900
ctttaaaagt gatgcacttt tcattatact gcatgtttt taattactaa acTTTGTt 24960
tttagagcag ttttaggttc acagccaaat tcccgTCTACt ctggccccac tggccactcc 25020
ccaggcccccc gccccTGGCC atgcataGCC tcccctacta tcaacatctc gcaccagaat 25080
ctgtacccac attgacacat catcatccag agtccacagt ttacatgagg gttctcttt 25140
gctgttgcattt accTGTACATA cagttacatt tgcgtccagag cagtgtttc ctgaaatcc 25200
atggTTTGTt tattttttta atgtatTTGA gacagaggct tgctctgtca cccaggcagg 25260

-continued

agtgcagtgg tgtgatctca gttcattgt aacctccaccc cttgggatca ggcaatcctc 25320
 tcacccctcgc ctcccgagta gctggaaacta tgggttatgag ccaccacact tggctaattt 25380
 ttaaattttt ttgttagagac agggtctaac catattgcac agtctggtct tgaactcctg 25440
 gcctcaagcg atccttctgg cttggcctcc caaagtacta ggattacaga tgtgagccac 25500
 tggccccgc tcatacggtttt attttagtg ctagaaagat actatgttat cattaaacg 25560
 atctgtttga aaatttgtac tttttgctgg atgcagtgc acgcgctgt aatcccagca 25620
 cttggggagg ccgggtgggg aggtagatca cgaggtcagg agatcgagac catcctggct 25680
 aacacccgtga aaccccgctc ctactaaatg tactaaaaaa attagtcggg cgtggtggcg 25740
 ggcacccgtta gtcccgacta ctcaggaggc tgaggcagga gagtggcgtg aacccaagag 25800
 gtggagcttgc agtgcgtgc actgcactcc agcctggca acagagttag 25860
 actccatctc aaaaaaaaaa aaaaaaattt gtactttta ataaaagtct ctggttctg 25920
 ggcattttaa atgttaggaat ttaattttact ttaagctcat ggagggatatt tagagcgtt 25980
 aaagaaatgg aaagaacaga actgggctcc ctttgtatg tcttcagagg gaagacaagc 26040
 ggagcgcgcct cctgcactac ctgaagggtgt gcctgttgca tctgtttcc ttttagtgcct 26100
 caaaaaacatt gaggttggtc aggcatagaa aaagatcaga ttgttgcata tcacacttgg 26160
 agtttacaaa gcacgttccc gtacgttac ttgggtggagc ttccctggtcc ccagtgccta 26220
 gcaaggcagg tggcatcatc ctggcttcac aaacaaggag agactgaggc cagagctcaa 26280
 gcccagccct ctgccttgca tccagttttg gcttcctgca cctccctgc tctgtggtag 26340
 caaaaaggctc ccacacattt aagttaccag gtgttggatt tagtcagtaa cctctattat 26400
 aagaaatgga tacttgaat gtctactcct tcaggacact tcgagaggtt gggctgcagt 26460
 catcacccggggctc tgggtgcgtc tgggtgaggc ccttgccttc actgtgaaact tgaaagatca 26520
 gtgtgacagt ttcttcctcataa agtgcatac ccatctgaag accatagctt tttttttttt 26580
 ttcttctatct tttttttgtat agattcaggc tctcaactatg ttgcccacg agtacttaaa 26640
 ctccctggctt caaatgaccc tcccacccctt gtcctccaaa gtcgtggaaat tacagggtgt 26700
 tgcgttccatc tccagtccttcc ataatctttt aatttcctccg atttttagaaat aagtcagtt 26760
 taactgtatgt gtgtgatcc gtttctcatt tgcgttccatgt ttgtatggcat ccgcattgcct 26820
 ggtccctatac ccgagactgt aagagcaggc tctctggagc ctggcatcgt ggggtggccc 26880
 tcagttcccc cactcaactgt gggaaagtttc ctttagtgc tgcgttccatgt ttccatcc 26940
 gttgcctgag gataaacctg cttcaggatt gttggtaaa agacttccct cacctagtt 27000
 ctgttaacgcc actgcgttcc accactgtgt agtactgttt gtttgcattt ttgggtgcata 27060
 ttcatttttta ccagaaatgt aagtcgttgc aggtcagaca gccactaaat ggcagaccc 27120
 ggatttgcac ccagaactct gtcgtgggtt caactgtgtt cttcccaaaag gtcgtgggtt 27180
 aaatattgcac ggctttctgg gacttcgtt ctctggcactt tactcaactgt ttgcacccctt 27240
 acaatagctt cagacagtttac taaacacgtt ggggtggctt gtcgtgggtt agtgcattt 27300
 gcaaaaaacag gcagcaaccc ggcctcgcc ctcagggttg tgcgttgcata cctgtgtccct 27360
 gtgtcttttg tttttttttt ttttttgcata cagagtctct ctctgttgcata cagggtggag 27420
 tacagtggca cgtatgtgc tcacggcaag ctccgcctcc cagggttgcacg ccattctcc 27480
 gtcgttccatc cccaaatgtt gtcgtgggtt ggtggccatc accacgcgtt gtcgtgggtt 27540
 tgcgttccatc cccaaatgtt gtcgtgggtt ggtggccatc accacgcgtt gtcgtgggtt 27600
 cttgtgtatct gcccctccat gtcgtgggtt tacagggtgtt agccactatg 27660

-continued

cccagcccccc cgcccttttt tttttttttt tttttttttt tttgagacgg agtcttgctc 27720
 ttcacccagg gctgaagtgc agtgacgcat ctccggctcac tgcaacacctcc gcctccggg 27780
 ttcaagtgtat tctccctgtct cagccctcctg aatagctggg attacaggta ctggccgcca 27840
 ggcccagcta atttttgtat tttttttttt ttttttagta gaggcggggtt ttcaccatgt 27900
 tggtcaggct ggtcttgaaa tcctgaccc tc aggtgatcca cctgccttgg cgtcccagag 27960
 tggtggaaatt accggcatga gccactgcat ccggcttccc attgctttt ctctgaagag 28020
 actttaagac ttggagttctg gttaaaaaaa aataaaagaaaa taaaaatcaa tgcccttgc 28080
 tgggtgaacg ggaagtgtaa aatctgaatt cgctataggg tcacaatccc agcctccagt 28140
 tcgcacagtg ccttcctggc gctgatgggg tgcatgttct gtcttcgcca ctaggtggag 28200
 geagttggta accttaaacc tttgtttctc cgtggtaaaa agtctgacaa gaaccgtaga 28260
 accttaaagc atattnaacc agtttaagcc ctgtttgcca tgttttagcc acaaagatac 28320
 tgttcagtga accatttaca gttgtgcctc cgcgttgtccc actctcagct gtgcacatca 28380
 ctgtcgctct ggaagaccta gcccagccag tttctaggtt agcatttgaa atggtcttgg 28440
 cctggtttaa ccatcagtaa atgaggccag attatgatata accttttccc ctcaaactag 28500
 ggatcccttt tttctctaca atagttaaat tggaaattgt ttatgtactc tattcattta 28560
 ttttggggg tgacctgatt ttttaaattt ttttagattt tcaagcacag tagtgagaag 28620
 aggagaaaaga gtagaacaag gtgttaactgc ctgtgaacga tcaattgaga taactcactg 28680
 ccttcgacca gcagtggctt ggtttctaat gacagtaaga caagttccctaa tagccattgt 28740
 taatctcctt ggaaaagaaaa tgaacactgt gtggtttcag aagctcattaa atatagcaga 28800
 agcactctgc ttctgttgc agggagggtt tcaagatgtat ttttctgcgtt gttcattgaa 28860
 cagacgtttc ctaagctctt ccttagtgcc tggcactggg aacagaagaa ggaagaagag 28920
 aaagctgtgc ctcagggtg ttctcaggc tc cgcactgagc ggtggtgacc agageccaccc 28980
 gcctgcctgc gtggccgggtg catcaggata gagcaggagt tcacagagga gctttgtcac 29040
 ttcccccctcc gctaaatctg ttctgtggcc ccacatcaact gagggtgtc accatcatcc 29100
 agtcacactgg gacaggcagc tgggagtcat ccttgaagcc tccctcaccta ggccttcatt 29160
 gcaaacctcc atttcctctg gatcaactgtc accagcctag tgcaggcacc accagctct 29220
 acccagagag cagggttcatt tccatctct tctggtecca gcccaacttc tgcgtcaagg 29280
 ccagaccgca gagggttcca ggccccgtga catggagttc agcgtgaccc tcaagggtctg 29340
 gagagagttg gcaagggttt tccatggggaa actggctatg ccctgttttgcactctggac 29400
 agttagcttt tgggtgttgg gcatggatcg aaggggcgca cagccggaaag ggagagctgt 29460
 aatcatgcag agatccctcc cctttaaagc aggggacagg cgagaaagga gatcgagtc 29520
 agaatgggtt ttgggtccct tgacctcaca cttcagggtt gcttcctgtg tgccatggat 29580
 atcattggcc agacagggac tcatgaagac ccagcctttt taaagagtaa acaataaaca 29640
 aggaaatgaa atgttcatacg attgtgatag attgtatcaa tgctgcgagg gcagtaaata 29700
 gaatgcgggtg atagagtcaa tagaggtacc taatttgggg aggtgggggtt ggtcagat 29760
 accctctctg aggggtttt gttgtatgtc aaactgaagg agcaaggaaac tggaaagagc 29820
 tggtctctgg gtggagggag cagcccttga gcttcctgtc gagcaggaga gaacgtttg 29880
 tatacagtaa gggaaagctcc aggtgggaga gtgatagggaa tgggtgttggg gagggaggtt 29940
 aggctctgtg tgcagtggag aggctggta ctacctgtc tggaggggca gagctcagg 30000

-continued

catccatgct taagagtccc agttttggta ttatatttgc caagaaatag ccaaccggcg 30060
ggcctggagg tgccccggatg cggaaggaaa gtagtccttg agagggaaatg tggtttctac 30120
ctgcacacgc acactcacat gcataccgc ctccattacg ttgtgtgtg gttgttttg 30180
aggcatcaga gggtgtgcgt gcccacat gttgattggg gtggcttcg cgttcagcgc 30240
tgcgcgcattcc cttcaccctt cccggcact tcagaattga cacttgagct ttgtgtaaa 30300
tagtgatgtg agtaactgtc attcaccgc acatccccca acacttaaag tcttagcagc 30360
tgcatttaac tcacgcataat ttgtttcatt ctaacagtgg tttctgtcac ccttgctct 30420
gcacagttt aaaaataacct ttgttaggggg cttctaagag cttggagtgc ctagtaaatg 30480
tttttgaatg gttagctaca gtgttgggtt tatatgtgt aatagtgaat ttaattggta 30540
agtaatcgctc tttctcgta catagcccat taggatgtca cctttctgt ttctactttg 30600
caggtcatta cacctactct gagaatcggt tgaaaaaaga cggcctgatt cttacaagcc 30660
gggggcctgg gaccagcttc gagttgcgc ttgcaatttg tgaagccctg aatggcaagg 30720
aggtggcggc tcaagtgaag gctccacttg ttcttaaaga ctagagcgc gaactgcgcac 30780
gatcaacttag agaaacaggc cgtaggaat ccattctcac tgtgttcgct ctaaacaaaa 30840
cagtggttagg ttaatgtgtt cagaagtgc tgcccttact acttttgcgg aagtatggaa 30900
gtcacaacta cacagagatt tctcagccta caaattgtgt ctatacattt ctaagccttg 30960
tttgcagaat aaacagggca ttttagcaaac tactgatttg ttctgtttt gtctctcatt 31020
tctttgtga aattaaattc cgtagcacct tcatttgcgc ctcttaactg tccatatggc 31080
actgaaataa aagaacagtg accacattt acacagcaag gaggaaaggc atacaacag 31140
aatttaagag gcttgcgtt ttctctgctt attagctgtg tgtttttaat gtgctattaa 31200
aaaaataccaa tgagg 31215

<210> SEQ_ID NO 2

<211> LENGTH: 189

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Met Ala Ser Lys Arg Ala Leu Val Ile	Lys Gly Ala Glu Glu
1 5	10 15

Met Glu Thr Val Ile Pro Val Asp Val Met Arg Arg Ala Gly Ile Lys	
20 25	30

Val Thr Val Ala Gly Leu Ala Gly Lys Asp Pro Val Gln Cys Ser Arg	
35 40	45

Asp Val Val Ile Cys Pro Asp Ala Ser Leu Glu Asp Ala Lys Lys Glu	
50 55	60

Gly Pro Tyr Asp Val Val Leu Pro Gly Gly Asn Leu Gly Ala Gln	
65 70	75 80

Asn Leu Ser Glu Ser Ala Ala Val Lys Glu Ile Leu Lys Glu Gln Glu	
85 90	95

Asn Arg Lys Gly Leu Ile Ala Ala Ile Cys Ala Gly Pro Thr Ala Leu	
100 105	110

Leu Ala His Glu Ile Gly Phe Gly Ser Lys Val Thr Thr His Pro Leu	
115 120	125

Ala Lys Asp Lys Met Met Asn Gly Gly His Tyr Thr Tyr Ser Glu Asn	
130 135	140

Arg Val Glu Lys Asp Gly Leu Ile Leu Thr Ser Arg Gly Pro Gly Thr	
145 150	155 160

-continued

Ser Phe Glu Phe Ala Leu Ala Ile Val Glu Ala Leu Asn Gly Lys Glu
 165 170 175

Val Ala Ala Gln Val Lys Ala Pro Leu Val Leu Lys Asp
 180 185

<210> SEQ ID NO 3
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic sequence

<400> SEQUENCE: 3

cuccacuugu ucuuaagat t

21

<210> SEQ ID NO 4
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic sequence

<400> SEQUENCE: 4

ucuuuaagaa caaggaggat t

21

<210> SEQ ID NO 5
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic sequence

<400> SEQUENCE: 5

cgcacgaucac uuagagaaaat t

21

<210> SEQ ID NO 6
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic sequence

<400> SEQUENCE: 6

uuuucucuaag ugaucgucgt t

21

<210> SEQ ID NO 7
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic sequence

<400> SEQUENCE: 7

ggaaguauugg aagucacaat t

21

<210> SEQ ID NO 8
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic sequence

<400> SEQUENCE: 8

uugugacuuc cauacuucct t

21

What is claimed is:

1. A PARK7 siRNA composition for inhibiting lung cancer metastasis, wherein the composition comprises a mixture of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8.

5

* * * * *